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ON THE ADSORPTION OF WATER VAPOUR BY CELLULOSE¹

By J. D. BABBITT²

Abstract

In this paper an attempt is made to gather together the best available data on the adsorption of water vapour by cellulose and to draw from this data a unified picture of the phenomenon. In the first place the various theories explaining the adsorption isotherm are tested. The Langmuir isotherm is shown to fit a small portion of the curve at low relative humidities, and the polymolecular theory of Brunauer, Emmett, and Teller is found to give agreement up to the point where capillary adsorption is assumed to become predominant. It is pointed out, however, that the assumptions involved in the theory of Brunauer, Emmett, and Teller are such that an equally satisfactory agreement might be obtained by assuming that the adsorption was confined to a monomolecular layer in which, owing to repulsive forces between neighbouring atoms, the adsorbing force varied with the number of atoms. Thus it is still doubtful whether the adsorption is monomolecular or polymolecular. The investigation shows that the adsorption on cotton is similar to that on wood, except for the fact that the internal surface area available for adsorption is less by a factor of 1.86.

An analysis is made of the data available for calculation of the heats of adsorption, and the values obtained from the different sources are compared. It is found that when the heats of adsorption are plotted against the relative humidity there is no appreciable difference between the values obtained with cotton and with wood. A mean value for the heats of adsorption is obtained. The relation between heats of adsorption and the latent heat of condensation is developed, and it is shown that there is an excess of internal energy in the adsorbed state over that of the liquid state.

Finally, an explanation is advanced to account for the experimental fact that there is a reduction in total volume when water vapour is adsorbed on cellulose. An attempt is also made to show (i) how the water molecule may be attached to the cellulose surface by hydrogen bonds in such a way that the energy will be greater than that in liquid water, and, (ii) that, on the basis of such a picture a volume contraction is to be expected.

The nature of the relation existing between cellulose and those molecules of water vapour that are adsorbed on its surface is not only of great practical importance in the paper and cotton trades, but a knowledge of it is fundamental for a proper understanding of the phenomenon of adsorption. The adsorption isotherm is, in this case, of the familiar sigmoid shape that is found for a large variety of materials. In particular it is especially interesting that protein substances such as hair, wool, wheat, etc., adsorb water vapour in this manner, so that it is justifiable to believe that the same mechanism of adsorption is involved and that any explanation obtained for adsorption by cellulose would also hold for this large and important group of substances.

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Yet at present, even though a vast quantity of experimental work has been done it is impossible to explain adequately the most elementary facts about this relation, and even such fundamental datum as the absorption isotherm itself has not been satisfactorily derived from a theoretical point of view; the cause of the sigmoid shape of this isotherm and of the pronounced hysteresis effect are to be considered the subject of conjecture rather than the consequence of an established theory. There are numerous isolated data that have so far refused to fit into any general treatment. It is hoped in this paper to discuss a few of these facts and, to some extent, to weld them into a co-ordinated theory.

One of the great difficulties involved in any study of the adsorption of water on cellulose is the fact that all cellulosic materials are microscopically porous bodies, and it is impossible to estimate from a priori considerations the area of surface that plays a part in the phenomenon. This is a serious drawback, as it prevents any simple calculation of the area of surface available per adsorbed molecule, and hence eliminates the most direct method by which monomolecular may be distinguished from polymolecular adsorption. It is therefore impossible to apply to adsorption by cellulose the methods of study by which Langmuir and others have so successfully attacked the problem of adsorption by certain metals. However, the fact that with cellulosic materials a large indefinite surface is involved has the advantage that the adsorption is correspondingly large, so that simple gravimetric methods are available for determining the adsorption equilibrium.

It has become apparent during the past few years that the concept of monomolecular adsorption developed by Langmuir is not adequate to explain completely the adsorption isotherm for an adsorption of this nature. It does appear as though the curve for the first few per cent of moisture adsorbed can be made to fit a Langmuir equation, but there is no tendency for that saturation at high pressures that is characteristic of Langmuir adsorption. On the other hand, there is reason to believe that the rapid increase of the adsorption at relative humidities approaching saturation is caused by capillary condensation. It is the section of the isotherm between these two regions that is interesting, for it is obvious that here simple monomolecular adsorption is not adequate, while the radius of the capillaries required for capillary condensation is so close to the actual diameter of a molecule that it is absurd to think of applying the Kelvin expression to this region.

Recently a theory has been put forward by Brunauer, Emmett, and Teller (5) that explains the sigmoid-type isotherm by assuming that the adsorption is not confined to a monomolecular layer but that it takes place in the second, third, and higher layers. By applying Langmuir's equation successively to these layers and summing, an equation is obtained that fits the curve very satisfactorily up to relative humidities where capillary adsorption becomes predominant. They assume that the cause of the sigmoid curve is polymolecular adsorption superimposed on a monomolecular layer developed at low pressures according to Langmuir's conceptions, and at high pressures

rapidly changing over to capillary condensation. There is some evidence, which will be outlined later, that the mechanism of polymolecular adsorption is not essential to explain adsorption of this nature, but Brunauer, Emmett, and Teller's theory will be developed on this basis and applied to cellulose in order to obtain a comparison with the experimental facts.

The Adsorption Isotherm

A typical adsorption isotherm for cellulosic materials is reproduced in Fig. 1. This has been taken from the measurements of Filby and Maass (10) and refers to white spruce wood at a temperature of 20° C. Both the adsorption and the desorption curves are given here and the hysteresis may be plainly seen. Curves of similar shape have been found for wood pulp, cotton, pure cellulose, wool, and in fact are common to all cellulosic materials and other swelling gels. This type of curve is not confined to those cases in which the adsorbate is water. Sigmoid curves are also found for the adsorption of various gases such as nitrogen, oxygen, argon, carbon monoxide, carbon dioxide, and butane (5), and the fact that such curves are found for all these gases immediately indicates that the explanation of the adsorption of water vapour by cellulose cannot be obtained from any special properties of the water molecule (such as its strong dipole moment). This also follows from the fact that when alcohols are adsorbed by wood, a curve of similar shape is obtained (17).

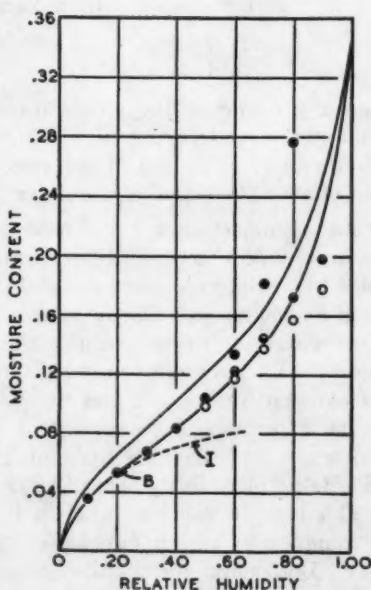


FIG. 1. Adsorption isotherm for spruce wood. Full lines, experimental data of Filby and Maass. I, Langmuir's equation. Points, Brunauer's equation; ●, $n = \infty$; ○, $n = 6$; ◐, $n = 7$.

Before developing the theory of polymolecular adsorption, it is interesting to study the simple Langmuir theory and to ascertain its possibilities and limitations. Langmuir's assumptions are that adsorption is confined to definite points of attraction on the adsorbing surface and that the adsorption is limited to a single molecular layer. By balancing the rate of adsorption on the surface against the evaporation he obtained (12) an equation in the form

$$\frac{x}{m} = \frac{abp}{1 + ap}, \quad (1)$$

where x = weight of adsorbed material,
 m = weight of adsorbent,
 p = pressure of vapour,

and a and b are constants.

This equation gives an isotherm that is hyperbolic in form, rising rapidly at low pressures but becoming parallel to the pressure axis as ap becomes large compared with unity. The curve exhibits a saturation effect at high pressures, the adsorbed mass not increasing further with increase of pressure. This is to be expected according to this theory when the monomolecular layer becomes complete. Since the adsorption of water on cellulose shows no such saturation effect, this type of isotherm obviously will not satisfy the water-cellulose relation at high pressures, but it is instructive to compare the theoretical with the low pressure portion of the observational curve.

The curve marked I in Fig. 1 is obtained from Langmuir's equation in the form

$$\frac{x}{m} = \frac{52.85 p/p_s}{1 + 4.95 p/p_s}, \quad (2)$$

where p_s is the saturation pressure at the temperature in question. It is immediately evident that up to a relative humidity $p/p_s = 0.20$ this equation fits the experimental isotherm of Filby and Maass very nicely. This corresponds to an adsorption of about 0.05 gm. of water per gram of wood.

In their work Brunauer, Emmett, and Teller have assumed that at the point B , which is the point of inflection of the experimental curve, the adsorption ceases to be confined to a monomolecular layer and that there adsorption begins in the second and higher layers. On the simple Langmuir theory, B does not mark the point where the monomolecular layer is complete, since this would not occur until the Langmuir curve reached saturation and became parallel to the pressure axis, but rather indicates the point at which it is no longer possible to fit the experimental curve with a Langmuir equation. The fact that the experimental curve deviates from this theory at the point B indicates that adsorption takes place in the second layer long before the first layer becomes filled. This is to be expected when it is considered that the molecules will not be completely free to move over the surface and that there will be a Maxwell-Boltzmann distribution over the different sites. Above the point B then, the adsorption will take place concurrently in the first and second layers until the first layer is complete.

It is interesting, on the basis of this equation, to determine the extent of the adsorbed mass if the monomolecular layer were completed. This is obtained by substituting $p/p_s = 1.00$ in Equation (2). The value of $\frac{x}{m}$ obtained is 8.9%. Thus it appears from these considerations that 8.9 gm. of water is sufficient to cover completely the surface of 100 gm. of cellulose. This is considerably greater than the value found for B .

Recently Brunauer, Emmett, and Teller (5) have generalized Langmuir's adsorption isotherm to cover multimolecular adsorption. By applying Langmuir's assumptions to the second and higher layers they derived the following isotherm equation for multimolecular adsorption on a free surface.

$$\frac{\frac{p}{m}}{(p_s - p)} = \frac{1}{(\frac{x}{m})_s C} + \frac{C - 1}{(\frac{x}{m})_s C} \cdot \frac{p}{p_s}, \quad (3)$$

where $\frac{x}{m}$ is the weight adsorbed per unit mass of adsorbent at pressure p and absolute temperature T ; p_s is the saturation vapour pressure; $(\frac{x}{m})_s$ is the mass of gas adsorbed when the entire adsorbent surface is covered with a unimolecular layer; and C is approximately equal to $e^{\frac{E_1 - E_L}{RT}}$, where E_1 is the heat of adsorption of the gas in the first adsorbed layer and E_L is the heat of condensation of the gas. If the function $\frac{p}{\frac{x}{m}(p_s - p)}$ is plotted against $\frac{p}{p_s}$ a straight line is obtained whose slope and intercept give the values of $(\frac{x}{m})_s$ and C .

If the adsorption takes place in a limited space, so that, at saturation pressure, only a limited number of layers can be adsorbed on the adsorbent, there is obtained the expression

$$\frac{x}{m} = \frac{(\frac{x}{m})_s C y}{1 - y} \cdot \frac{1 - (n+1)y^n + ny^{n+1}}{1 + (C-1)y - Cy^{n+1}}, \quad (4)$$

where $y = \frac{p}{p_s}$, $(\frac{x}{m})_s$ and C have the same meaning as before, and n is the maximum number of layers of adsorbed gas that can build up on the walls of the capillaries, supposedly of plane parallel sides. Equation (4) reduces to Equation (3) when $n = \infty$, and in the other extreme case when only one adsorbed layer can form on the surface, i.e., when $n = 1$, it reduces to the Langmuir type equation,

$$\frac{p}{\frac{x}{m}} = \frac{p_s}{C(\frac{x}{m})_s} + \frac{p}{(\frac{x}{m})_s}. \quad (5)$$

Brunauer, Emmett, and Teller have suggested that a rather plausible interpretation of the constant n is that the width of the pores, cracks, and capillaries of the adsorbent sets a limit to the maximum number of layers that can be adsorbed even at saturation pressure. It is conceivable that factors other than the diameter of the capillaries can place a limit on the

maximum number of layers that can be adsorbed, but Brunauer, Emmett, and Teller contend that Equation (4) should still remain valid.

In order to apply these equations to the experimental isotherm of Filby and Maass we shall start with Equation (3). To evaluate $\left(\frac{x}{m}\right)_s$ and C , $\frac{p}{x/m(p_s - p)}$ is plotted against p/p_s . This has been done in Fig. 2. The

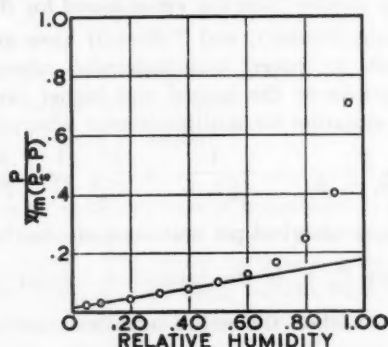


FIG. 2. Plot of $\frac{p}{x/m(p_s - p)}$ against p/p_s for spruce wood.

curve departs strongly from a straight line at high relative humidities, but up to 50% a linear relation is obtained. From the slope and intercept of the curve in Fig. 2 the following values are obtained for $\left(\frac{x}{m}\right)_s$ and C .

$$\left(\frac{x}{m}\right)_s = 6.17 \text{ and } C = 11.80.$$

On the basis of the fact that C is approximately equal to $e^{\frac{E_1 - E_L}{RT}}$, the value of $E_1 - E_L$ can be obtained from the relation

$$E_1 - E_L = \frac{2.303 RT \log_{10} 11.80}{18},$$

where $E_1 - E_L$ is the difference in the heat of adsorption in the first and subsequent layers per gram of water vapour. On this basis a figure of 80 cal. per gram is obtained. This result will be discussed further when the investigation of the heats of adsorption is described.

The values of $\frac{x}{m}$ obtained from Equation (3) by the use of these constants are shown in Fig. 1. These values deviate considerably from the experimental curve at high relative humidities as would be expected from Fig. 2. The rapid increase occurs at too low humidities although the similarity of the shape of the two curves indicates that some mechanism of this nature does take place in the vicinity of saturation.

The values obtained for $\left(\frac{x}{m}\right)_s$ and C can now be substituted in Equation (4). The results obtained from this equation for $n = 6$ and $n = 7$

are shown in Fig. 1. It is obvious that a value of n between 6 and 7 will give excellent agreement with the experimental curve up to relative humidities of 70% or more. Above this the experimental curve rises too steeply. There, capillary condensation undoubtedly occurs and it would be necessary to use some equation similar to Equation (3) but with the origin displaced.

At this point it is interesting to note that Equation (5) governing the Langmuir adsorption in the first layer, while being of the same form as Equation (2), does not have the same constants. It can be put in the form

$$\frac{x}{m} = \frac{C \left(\frac{z}{m}\right)_s p/p_s}{1 + C p/p_s}, \quad (6)$$

and substituting the values obtained for the constants C and $\left(\frac{x}{m}\right)_s$, the following expression is obtained.

$$\frac{x}{m} = \frac{72.9 p/p_s}{1 + 11.80 p/p_s}. \quad (7)$$

This curve coincides with the experimental data only for a small interval at low relative humidities; this indicates that the region in which the adsorbed molecules are confined to a monolayer is very small and that the adsorption in the second layer begins at a very early stage. It is interesting to note that the saturation value of Equation (6) is numerically very close to the point B in Fig. 1.

According to the above analysis the adsorption can conveniently be thought of as occurring in three distinct stages. First, at low humidities there is a small region where the adsorption may be considered as being monomolecular and where it proceeds according to Langmuir's mechanism. Secondly, there is in the second, third, and higher layers what may be called polymolecular adsorption and which can be treated in a manner similar to that adopted for monomolecular adsorption, but with the assumption that the energy involved is much smaller and is approaching that of the attraction of the free liquid. Finally, in the vicinity of saturation the adsorption proceeds by capillary attraction.

This hypothesis agrees with certain conclusions reached by Barkas (2, 3) from measurements on the shrinkage that occurs in wood exposed to different relative humidities and on changes in the strength of wood at different moisture contents. Barkas has distinguished between molecularly bound water and water retained by capillary adsorption. He concludes that until the moisture content is 6% all the water is molecularly bound. At 6%, capillary adsorption begins to occur but is not appreciable until the moisture content is about 16%, at which point his curves begin to deviate from the straight line corresponding to adsorption by molecular bonds only. If there were no capillary adsorption approximately 23 gm. would be adsorbed at saturation pressures. According to the theory of Brunauer, Emmett, and Teller the explanation of these facts is slightly different but is even more plausible. Their theory assumes that 6% is adsorbed in the first layer and up to 16% the adsorption is

still molecular but occurs in the second and higher layers, while above 16% the adsorption is largely caused by capillary attraction.

The fact that this theory of polymolecular adsorption gives such a good explanation of these experimental facts provides substantial support for the assumption that the adsorption is not confined to a monomolecular layer. It is essential, therefore, at this stage to point out that a monomolecular theory is not thereby ruled out. Δ In fact the essential point of the theory of Brunauer, Emmett, and Teller is that the force of attraction decreases after the first layer is filled. A similar effect might be obtained from monomolecular adsorption by assuming that a repulsion exists between the adsorbed molecules, so that, as the number of atoms in the monomolecular layer increases, the force attracting the molecules to the surface becomes less because of the mutual repulsion. Such a theory is very promising as it immediately gives a physical meaning to n , which then might be considered as the greatest number of near neighbours that any adsorbed atom might have. Such a force of repulsion between adsorbed atoms has in fact been found by Roberts (16); this will be discussed further when the heats of adsorption are considered.

Application to Cotton

It is also instructive to apply an analysis of this nature to cotton. For this purpose we use the data of Urquhart and Williams (22). In Fig. 3 the adsorption isotherm for soda-boiled cotton at a temperature of 20° C. has been reproduced. Again the hysteresis has been neglected as in the work on wood, and the study is confined to adsorption alone. In the same figure the points obtained by Filby and Maass for spruce wood are given, and the similarity in the shape of the two curves is immediately evident. However, the adsorption on the cotton is everywhere considerably less than that on the wood.

The equation of Brunauer, Emmett, and Teller will now be applied to this cotton isotherm. Proceeding in the same way as before and plotting

$$\frac{p}{x/m(p_s - p)} \text{ against } p/p_s, \text{ we obtain the following values for } C \text{ and } \left(\frac{x}{m}\right)_s.$$

$$C = 16.07 \text{ and } \left(\frac{x}{m}\right)_s = 3.32.$$

Substituting these values into Equation (4) and solving for $n = \infty$ and $n = 6$, we obtain the two sets of values plotted in Fig. 3. It is evident that once again the curve with $n = 6$ gives excellent agreement up to relative humidities of 70%. It follows that the same considerations hold for cotton as were outlined above for wood. There is, however, some information to be obtained from the differences in the two cases.

In the first place, it is found here that the monomolecular layer is saturated when the moisture content is 3.32%. For wood this figure is 6.17%. The relative humidities corresponding to these two cases are 24.3% and 25.7%, respectively. It is evident that the vapour pressure at which the surface becomes saturated with a monomolecular layer is the same for cotton as for

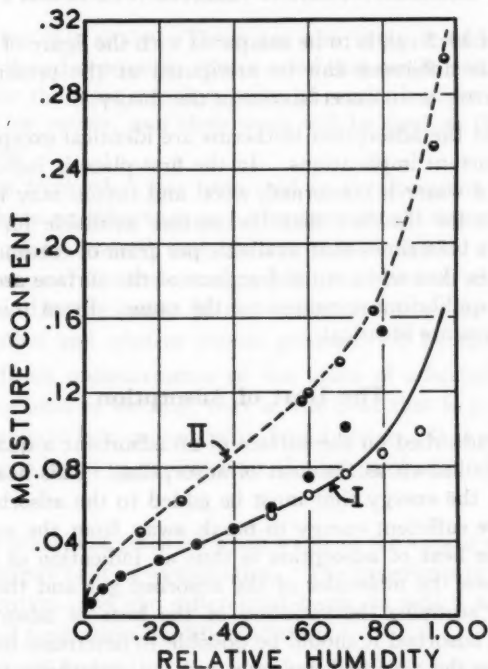


FIG. 3. Comparison of isotherms for cotton and spruce wood. Full line, I, cotton (Urquhart and Williams). Broken line, II, = full line $\times 1.86$. \odot , Spruce wood, experimental data of Filby and Maass. Points \circ and \bullet are for $n=6$ and $n=\infty$, respectively, in Brunauer's equation.

wood. This indicates that the binding force between the water molecule and the cellulose is the same in the two cases. The fact that the cotton is saturated with a monomolecular layer with only 3.32% adsorbed, while wood requires 6.17%, indicates that the surface available in the case of cotton is only $\frac{3.32}{6.17} = 0.538$ that of the wood. This is interesting. It

means that if the adsorptions obtained for cotton are multiplied by $\frac{1}{0.538} = 1.86$ a curve would be obtained similar to that for wood. This has been done and the curve is virtually identical with the curve of Filby and Maass as shown in Fig. 3. There is one difficulty in this hypothesis, however. The value for C obtained on the basis of the theory of Brunauer, Emmett, and Teller is not the same for cotton and for wood. For spruce, the writer found $C = 11.80$ and for cotton it is equal to 16.07. Since C is approximately equal to $e^{\frac{E_1 - E_L}{RT}}$ this indicates that E_1 cannot be the same in the two cases. Evaluating $E_1 - E_L$ for cotton we obtain

$$E_1 - E_L = \frac{2.303 RT \log_{10} 16.07}{18} = 89.5 \text{ cal.}$$

This figure of 89.5 cal. is to be compared with the figure of 80 cal. obtained for wood. This difference can be attributed at the present time only to experimental error, or to uncertainties in the theory.

This fact that the adsorption isotherms are identical except for a constant factor has important implications. In the first place it indicates that as far as adsorption of water is concerned, wood and cotton may be considered as identical except for the fact that the surface available for adsorption per gram of wood is 1.86 times that available per gram of cotton. In the second place it indicates that when equal fractions of the surface are covered in the two cases the equilibrium pressures are the same. From this it follows that the binding forces are identical.

The Heat of Adsorption

When gas is adsorbed on the surface of an adsorbent a quantity of heat is set free which is known as the heat of adsorption. This heat of adsorption is a measure of the energy that must be added to the adsorbed gas in order that it will have sufficient energy to break away from the attraction of the adsorbent. The heat of adsorption is thus an indication of the strength of the bond between the molecules of the adsorbed gas and the surface of the adsorbent. By studying the variation of the heat of adsorption with the quantity of gas adsorbed it should be possible to determine how the strength of bond between the adsorbed molecule and the underlying lattice is related to the adsorbed mass. In particular it might be expected that some indication would be found in the heat of adsorption if the adsorption changes from monomolecular to polymolecular. This point has been brought out in Brunauer, Emmett, and Teller's theory, and a value has already been obtained for the difference to be expected between the heat of adsorption and the latent heat of condensation. It is interesting therefore to examine all the data available in order to ascertain how their assumptions are supported.

The information available on the heats of adsorption of cellulose is not extensive, and in order to obtain a complete picture it is necessary to piece together data from different sources. The direct measurements are confined to some on the integral heat of adsorption of cellulose by Katz (11), similar measurements on prepared wood fibre by Volbehr, which are also quoted by Katz (11), and a series of determinations by Argue and Maass (1) on the heat of wetting of cellulose by water. Fortunately it is possible, by the use of the Clausius-Clapeyron equation, to calculate the heats of adsorption from vapour-pressure-adsorption equilibrium data. If two adsorption isotherms are obtained at temperatures not too far apart the heat of adsorptions can be quite easily determined. There is no reason to believe that this method does not give accurate and true results, and it has been used extensively in the calculation of the heat of adsorption for other materials. Stamm and Loughborough (20) have applied this method to a mass of data that they have obtained for the equilibrium of Sitka spruce and water vapour and these data

are available for this study. There are also some results of Pidgeon and Maass (15) on the adsorption by spruce wood that can be used for this purpose. However, by far the most complete series of results is given by Urquhart and Williams (22) for cotton, and their work will be used as the main basis for our calculations.

It is obvious from what has been said in the foregoing section that the binding force between adsorbate and adsorbent should depend on the fraction of available surface covered and, as was shown, this is a function of the equilibrium pressure; for the same pressure the heats of adsorption of wood and cotton should be the same. In the work that follows the relation between heat of adsorption and relative vapour pressure will be considered.

In all the direct measurements of the heats of adsorption the quantity measured is the heat of wetting, that is, the heat that is given off when the adsorbent is brought into contact with liquid water. It is assumed that this heat of wetting is equal to the net heat of adsorption, defined by the relation

$$\lambda_n = \lambda_t - L,$$

where λ_t is the total heat given off when water in the vapour phase is adsorbed and L is the latent heat of evaporation. The experiments give the integral heats of adsorption, and the differential heats, in which we are interested, can be obtained from these by differentiation.

Katz in his work found that the curve relating the integral heat of adsorption with the amount adsorbed could be expressed by an equation of the form

$$W = \frac{A \frac{x}{m}}{B + \frac{x}{m}},$$

where W is the integral heat of adsorption and A and B are constants. He found that for cellulose and prepared wood fibre these constants had the following values.

	A	B
Cellulose	11.6	0.030
Prepared wood fibre	23.62	0.0895

The differential heat of adsorption can be obtained from these equations by differentiation. Thus,

$$\lambda_n = \frac{dW}{d(\frac{x}{m})} = \frac{AB}{(B + \frac{x}{m})^2}.$$

In Tables I and II below, the values obtained from this equation for λ_n in the case of cellulose and prepared wood fibre respectively are given.

The values for $\frac{x}{m}$ given in Tables I and II have been derived from the relative humidity by means of Figs. 3 and 1 respectively. Katz does give an isotherm for cellulose from which it would have been possible to determine the relation between $\frac{x}{m}$ and the relative humidity, but it was found after trial that there was little difference in the curves, and the values of Urquhart

TABLE I

DIFFERENTIAL HEAT OF ADSORPTION FOR CELLULOSE TAKEN FROM
DATA OF J. R. KATZ

Relative humidity, %	$\frac{x}{m}$	$\lambda_n = \frac{0.348}{(0.030 + \frac{x}{m})^2}, \text{ cal.}$
0.0	0.000	387
2.0	0.009	232
5.0	0.015	174
10.0	0.022	129
20.0	0.030	98
30.0	0.039	74
40.0	0.047	58
50.0	0.055	48
60.0	0.065	38
70.0	0.077	30
80.0	0.095	22
90.0	0.128	14

TABLE II

DIFFERENTIAL HEAT OF ADSORPTION FOR PREPARED WOOD FIBRE TAKEN
FROM DATA OF J. R. KATZ

Relative humidity, %	$\frac{x}{m}$	$\lambda_n = \frac{2.114}{(0.0895 + \frac{x}{m})^2}, \text{ cal.}$
0.0	0.000	264
2.0	0.009	216
5.0	0.021	173
10.0	0.035	135
20.0	0.054	103
30.0	0.068	85
40.0	0.084	71
50.0	0.100	59
60.0	0.120	48
70.0	0.141	40
80.0	0.173	31
90.0	0.225	21

and Williams gave a slightly smoother relation between relative humidity and heat of adsorption. The results in Tables I and II have been plotted in Fig. 4.

Argue and Maass in their work (1) give directly the total heat of adsorption of water vapour adsorbed on a cellulose prepared from pure cotton. The experimental method was similar to that used by Katz but they have handled their results in a slightly different manner. The results have been reproduced in Table III. The values of the relative humidity given in the second column of Table III were obtained from the adsorption curve of Urquhart and Williams, which is reproduced in Fig. 3. There is a possibility that the cellulose used by Argue and Maass would have an adsorption isotherm differing slightly from

this curve, but since they do not give adsorption data for their cotton the curve of Urquhart and Williams is used. The data from Table III have been plotted in Fig. 4.

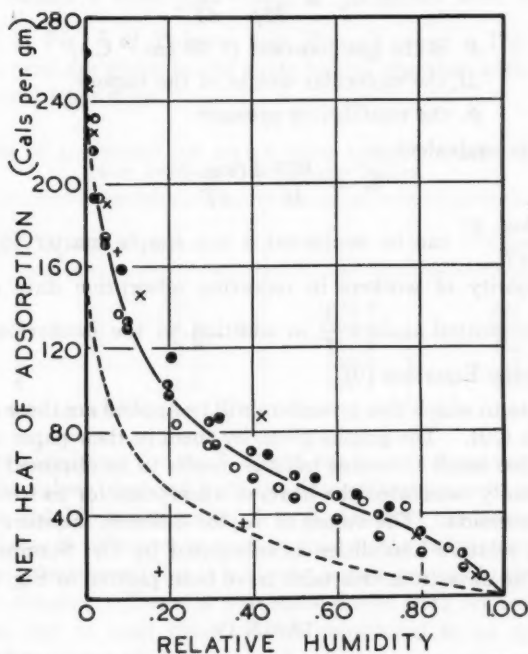


FIG. 4. Heats of adsorption. ● Cotton (Argue and Maass). X, Spruce wood (Stamm and Loughborough). +, Spruce wood (Pidgeon and Maass). ○, Cotton (Urquhart and Williams). ●, Cellulose (Katz) ○, Prepared wood fibre (Katz). -----, Free energy, $\frac{RT}{M} \log \frac{p_s}{p}$.

TABLE III

DIFFERENTIAL HEATS OF ADSORPTION FOR COTTON CELLULOSE AT 25° C.,
TAKEN FROM DATA OF ARGUE AND MAASS

Moisture content, %	Relative humidity, %	λ_1 , cal.	λ_2 , cal.
0.00	0.0	832.0	250.0
0.005	1.0	814.0	232.0
0.01	2.4	775.0	193.0
0.02	8.9	740.0	158.0
0.03	20.9	697.9	115.9
0.04	32.0	668.9	86.9
0.05	43.7	651.6	69.6
0.06	55.0	639.9	57.9
0.07	64.7	631.7	49.7
0.08	72.3	625.5	43.5

As mentioned above, it is possible to calculate the heats of adsorption from adsorption data by use of the Clausius-Clapeyron equation. This equation can be written in the form

$$\lambda_t = \frac{RT^2}{Mp} \frac{dp}{dT}, \quad (8)$$

where

R is the gas constant (1.98 cal./° C.),

M , the molecular weight of the vapour,

and

p , the equilibrium pressure.

Equation (8) is equivalent to

$$\lambda_t = \frac{RT^2}{M} \frac{d(\log_e p)}{dT}, \quad (9)$$

so that if $\frac{d(\log_e p)}{dT}$ can be evaluated it is a simple matter to calculate λ_t .

Since the majority of workers in reporting adsorption data give isosteres where $\log p$ is plotted against $\frac{1}{T}$ in addition to the isotherms, there is no difficulty in using Equation (9).

The first data to which this procedure will be applied are those of Stamm and Loughborough (20). The graphs given by them in their paper unfortunately proved to be too small to enable reliable results to be obtained but Dr. A. J. Stamm has kindly calculated the heats of adsorption for us from the original data in his possession. The values of λ_a for different moisture contents and corresponding relative humidities as calculated by Dr. Stamm are given in Table IV. The data from this table have been plotted in Fig. 4.

TABLE IV
DIFFERENTIAL HEAT OF ADSORPTION CALCULATED FROM DATA OF STAMM
AND LOUGHBOROUGH FOR SITKA SPRUCE WOOD AT
A TEMPERATURE OF 20.0° C.

Moisture content, %	Relative humidity, %	λ_a , cal.
0.5	1	246
1.0	2	225
2.0	5	190
4.0	13	146
8.0	42	88
16.0	79	30
24.0	93	10

It is also possible to calculate the heat of adsorption of spruce wood from some data given by Pidgeon and Maass (15). They measured the adsorption equilibrium at several different temperatures and have calculated adsorption isosteres, so that it is possible to apply the same procedure to their results as has been used above in the case of Stamm and Loughborough. It is true that these measurements of Pidgeon and Maass have been found by both Urquhart and Williams and Filby and Maass to be too low at high humidities,

but since their results below 70% relative humidity agree substantially with those of Filby and Maass it should be allowable to use them for our purpose.

In order to obtain a value for $\frac{d(\log_e p)}{dT}$, tangents were drawn to the isosteres given in Fig. 7 of Pidgeon and Maass's paper. The values were taken at 20° C. and are given in the table below, together with the heats of adsorption derived from them.

TABLE V
HEATS OF ADSORPTION FOR SPRUCE WOOD AT 20° C. CALCULATED
FROM DATA OF PIDGEON AND MAASS

Moisture content, %	p/p_s , %	λ_i , cal.	λ_s , cal.
1	2.1	1276.0	691.1
2	4.8	1190.0	605.1
3	8.0	751.0	166.1
5	17.8	598.0	13.1
8	37.8	620.4	35.5

The values obtained here for the 3, 5, and 8% moisture content are roughly equivalent to the values obtained from the data of Stamm and Loughborough. The values at 1 and 2% are much larger. A glance at the isosteres given by Pidgeon and Maass is sufficient to explain this, as the points used in plotting the isosteres are so scattered that it is almost impossible to obtain an accurate estimate of the tangent. There is also some doubt with regard to the 3, 5, and 8% curves, but at least these can be considered to be approximately correct. They have been plotted in Fig. 4.

Finally, the data of Urquhart and Williams (22) can be used to calculate the heats of adsorption for soda-boiled cotton. Since they give $\log p$ plotted against $\frac{1}{T}$ in their Fig. 4 it is possible to apply the Clausius-Clapeyron equation as given in Equation (9) directly to their work. The values obtained in this way for a temperature of 20° C. are given in Table VI.

The figures in Table VI have been plotted in Fig. 4 along with the rest of the heats of adsorption. It is to be seen from this figure that the data from the different sources agree fairly well with the exception of a few isolated points, and it may be assumed that this disagreement is the result of experimental error. It is especially interesting to note that when the heats of adsorption are plotted in this way there does not appear to be any significant difference between those obtained from cotton and those obtained from wood. This supports our hypothesis that the adsorption in these two cases is similar and differs only in the area of surface available for adsorption. A mean curve has been drawn through the points in Fig. 4, and this may be taken as representing the variation of the heat of adsorption with relative humidity.

TABLE VI

DIFFERENTIAL HEATS OF ADSORPTION OF SODA-BOILED COTTON AT
20° C., FROM THE DATA OF URQUHART AND WILLIAMS

Moisture content, %	Relative humidity, %	λ_1 , cal.	λ_2 , cal.
1.2	3.2	778	193
1.9	8.0	722	137
3.1	22.0	669	84
3.8	29.8	659	74
4.3	35.8	648	63
5.2	46.0	638	53
6.1	56.0	628	43
7.2	66.3	631	46
8.7	76.5	628	43
11.5	86.8	608	23
15.7	95.0	595	10
19.9	98.7	590	5

It is to be noted that this curve gives an initial heat of adsorption at zero vapour pressure of approximately 280 cal. This is in excellent agreement with the value of 289 cal. given by Neale and Stringfellow (13), who have investigated the adsorption of water vapour by cotton at very low relative humidities.

The curve in Fig. 4 exhibits the same general tendencies as a curve given by Williams (23) for the heats of adsorption obtained when sulphur dioxide is adsorbed by charcoal. Both curves fall rapidly with increasing relative humidities at low humidity, flatten out in the middle humidity region, and then fall more rapidly to zero as saturation is approached. Since the isotherm for the adsorption of sulphur dioxide on charcoal also has a sigmoid shape it may be that all heats of adsorption pertaining to this type of isotherm are of a similar nature. It is, however, interesting to note that Williams' curve shows a definite maximum before the final fall to zero and also there seems to be an indication that in his case the heat of adsorption becomes zero before saturation pressures are reached.

The Thermodynamics of Adsorption

It is obvious that the adsorption of a vapour is a phenomenon that is closely related to condensation. We have assumed this in the discussion of the experimental work on the heats of adsorption and have defined the net heat of adsorption as the total heat minus the latent heat of condensation. It is therefore instructive to follow up this idea and to determine as closely as possible the relation that exists between the heat of adsorption and the heat of condensation. Many workers have expressed such relations but since it is difficult to find an explicit derivation, this matter will be considered in some detail.

In its thermodynamical aspects, adsorption is very similar to solution, and a great deal of the theory of dilute solutions can be applied to adsorption.

This forms the basis of the work given below, in which the relation between heat of adsorption and heat of condensation is shown.

Let us first of all consider a mass of adsorbing material of sufficient size so that the removal of unit mass of adsorbate will not noticeably affect the adsorption ratio. It is assumed that the adsorbed mass is $\frac{x}{m}$ grams per gram of adsorbent and that the equilibrium vapour pressure of the adsorbate is p . It will be considered also that the external hydrostatic pressure on the adsorbent is p , that is to say, the system is under its own vapour pressure. On the other hand, we shall consider a quantity of the liquid adsorbate also under its own pressure, which in this case is equal to p_s , the saturation vapour pressure at the temperature T .

We wish to bring the adsorbing system into equilibrium with the liquid adsorbate and in order to accomplish this we shall increase the external hydrostatic pressure on the adsorbent to a value $P + p$ such that the vapour pressure over the adsorbent becomes equal to p_s . (The value of $P + p$ can be determined from the equation,

$$\frac{dp}{dP} = \frac{s}{v},$$

where s is the volume occupied by the adsorbate in the adsorbed state and v the volume in the vapour state. See, for instance, O. Sackur: "Thermochemistry and Thermodynamics": Trans. by G. E. Gibson, pp. 219-220. 1917.) P may be considered as the swelling pressure and is similar to the osmotic pressure of solutions.

The adsorbent and the liquid adsorbate can now be brought into contact by the arrangement shown in Fig. 5. The adsorbent is separated from the

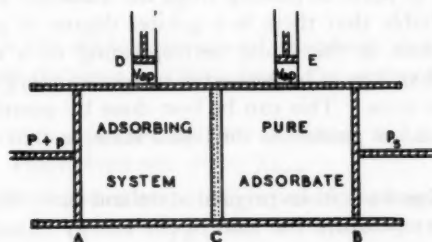


FIG. 5

liquid adsorbate by a semipermeable membrane C that is permeable to the adsorbate but not to the adsorbent. The adsorbent is confined by a piston A on which the pressure is $P + p$, and the adsorbate by a piston B on which the pressure is p_s . A lateral cylinder leads off from each chamber and is separated from the chambers by diaphragms permeable to the vapour alone. The pressures in these lateral cylinders are maintained at p , by the pistons D and E . The whole system is thus in equilibrium and we may consider the following cycle in which all the steps are reversible.

(1) Unit mass is evaporated from the liquid adsorbate and removed by means of the lateral cylinder. The pressure is maintained at p_s by piston B . The heat added to the system during this step is equal to L , the latent heat of evaporation under pressure p_s .

(2) The unit mass of vapour is transferred to the adsorbent by means of the second lateral cylinder, and there it is adsorbed. The heat involved in this process is λ_{P+p} , which is the heat of adsorption at pressure $P + p$.

(3) Unit mass of adsorbate is transferred from adsorbent to the liquid adsorbate through the semipermeable membrane C by movement of the pistons. The work done

$$dw = - \int_{P+p}^{p_s} s dp,$$

where s is the volume occupied by unit mass of the adsorbate. Now we have $\frac{ds}{dp} = \kappa$, the compressibility of the adsorbate, and we may assume that κ is a constant. Hence $s = \kappa p$.

Thus

$$\begin{aligned} dw &= - \int_{P+p}^{p_s} \kappa p dp \\ &= - \frac{\kappa}{2} [p_s^2 - (P+p)^2], \end{aligned}$$

and since p_s and p are small compared with P

$$dw = \frac{\kappa}{2} P^2.$$

Besides this work that is performed in transferring the adsorbate from the adsorbent to the liquid, it is necessary to recognize the possibility that there may be a change of state in passing from the adsorbed phase to the liquid phase. It is probable that there is a greater degree of organization in the adsorbed phase than in the liquid corresponding to a certain amount of solidification, so that it may be necessary to add an energy term corresponding to a change of state. This can be best done by assuming an increase in entropy equal to ΔS in passing to the liquid state, so that the energy change is $T \Delta S$.

The system is now back in its original state and since the cycle was carried out at constant temperature the sum of the energy changes involved must equal zero. Hence

$$L - \lambda_{P+p} + \frac{\kappa}{2} P^2 + T \Delta S = 0. \quad (10)$$

Under ordinary conditions an adsorbent is either under atmospheric pressure or the equilibrium vapour pressure, so that now the relation between λ_{P+p} and λ_p must be found.

In order to do this consider a quantity of adsorbent confined in a chamber fitted with a piston and a lateral cylinder as shown in Fig. 6. Here again the membrane separating the chamber from the lateral cylinder is permeable to the vapour only.

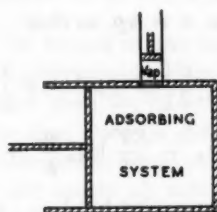


FIG. 6

We now consider the following reversible steps:

1. Unit mass of adsorbate is evaporated from the adsorbent and removed through the lateral chamber, the pressure being maintained at p by means of the piston. The heat added to the system is λ_p .
2. The vapour is compressed from pressure p to saturation pressure p_s .

$$\begin{aligned} \text{Work done} &= - \int_p^{p_s} v dp \\ &= - \int_p^{p_s} \frac{RT}{M} \frac{dp}{p} \\ &= - \frac{RT}{M} \log_e \frac{p_s}{p}. \end{aligned}$$

3. The adsorbing system in the chamber is compressed to a pressure $P + p$ by means of the piston.

$$\text{Work done} = - \int_p^{P+p} (V - s) dp,$$

where V is the original volume of adsorbent plus adsorbate and s is the volume decrease resulting from the removal of unit mass of adsorbate.

4. The vapour is adsorbed on the adsorbent by means of the lateral cylinder. Heat given out = $-\lambda_{P+p}$.
5. The adsorbent plus adsorbate is expanded to original pressure p .

$$\text{Work done} = - \int_{P+p}^p V dp$$

The system is now in its original state so that the sum of the energies must equal zero. Thus

$$\lambda_p - \frac{RT}{M} \log_e \frac{p_s}{p} - \int_p^{P+p} (V - s) dp - \lambda_{P+p} - \int_{P+p}^p V dp = 0,$$

$$\text{which becomes } \lambda_p - \frac{RT}{M} \log_e \frac{p_s}{p} + \int_p^{P+p} s dp - \lambda_{P+p} = 0.$$

But now we have, as before, $s = \kappa p$, so that

$$\int_p^{P+p} s dp = \frac{\kappa}{2} [(P+p)^2 - p^2] = \frac{\kappa}{2} P^2.$$

Thus

$$\lambda_{P+p} = \lambda_p - \frac{RT}{M} \log_e \frac{p_s}{p} + \frac{\kappa}{2} P^2.$$

Substituting this into the expression for λ_{P+p} , we find

$$L - \lambda_p + \frac{RT}{M} \log_e \frac{p_s}{p} + T \Delta S = 0$$

or

$$\lambda_p = L + \frac{RT}{M} \log_e \frac{p_s}{p} + T \Delta S. \quad (11)$$

Remembering the definition of the net heat of adsorption λ_n , we find

$$\lambda_n = \frac{RT}{M} \log_e \frac{p_s}{p} + T \Delta S. \quad (12)$$

Now $\frac{RT}{M} \log_e \frac{p_s}{p}$ is simply the free energy of expansion of a gas from the pressure p_s to the pressure p . We shall calculate this for water vapour and compare the values obtained with those of λ_n given in Fig. 4. The difference between λ_n and the free energy will be equal to $T \Delta S$, which can be considered as the change in internal energy of the water vapour during the transition from the adsorbed to the free state. The value of $\frac{RT}{M} \log_e \frac{p_s}{p}$ for different relative humidities is given in Table VII, and these values have been plotted as the broken curve in Fig. 4.

It is interesting to note that when the free energy is considered as a function of the relative humidity, the resulting curve is independent of the nature of the adsorbent. It is only when the relation between free energy and moisture

TABLE VII
VALUE OF $\frac{RT}{M} \log_e \frac{p_s}{p}$ FOR 20° C.

Relative humidity, %	$\frac{RT}{M} \log_e \frac{p_s}{p}$, cal.	Relative humidity, %	$\frac{RT}{M} \log_e \frac{p_s}{p}$, cal.
0.1	222.6	40.0	29.9
0.5	170.8	45.0	26.1
1.0	148.4	50.0	22.6
2.0	126.1	55.0	19.6
4.0	103.8	60.0	16.8
5.0	96.8	65.0	14.1
10.0	75.3	70.0	11.7
15.0	62.0	75.0	9.3
20.0	52.6	80.0	7.3
25.0	45.3	85.0	5.4
30.0	39.3	90.0	3.4
35.0	34.3	95.0	1.6

content is considered that the nature of the adsorbent becomes important. This stresses once again the convenience of using the relative humidity as the independent variable rather than the moisture content.

Fig. 4 shows immediately that there is definitely a change of phase in passing from the adsorbed state to the liquid state. The experimental points for the heats of adsorption are nearly all well above the free energy curve and the difference between them and the curve is, at all relative humidities, quite appreciable. This difference has been calculated. It is shown in Table VIII and the resulting curve is given in Fig. 7.

TABLE VIII

Moisture content (cotton), %	Relative humidity, %	λ_n	$\frac{RT}{M} \log_e \frac{p_s}{p}$	$T \Delta S = \lambda_n - \frac{RT}{M} \log_e \frac{p_s}{p}$
0.5	1.0	230.0	148.4	81.6
0.9	2.0	210.0	126.1	83.9
1.5	5.0	173.0	96.8	76.2
2.1	10.0	136.0	75.3	60.7
2.5	15.0	113.5	62.0	51.0
2.95	20.0	98.5	52.6	45.9
3.4	25.0	87.8	45.3	42.5
3.8	30.0	79.2	39.3	39.9
4.3	35.0	72.1	34.3	37.8
4.7	40.0	66.0	29.9	36.1
5.1	45.0	60.0	26.1	33.9
5.6	50.0	54.7	22.6	32.1
6.0	55.0	49.9	19.6	30.3
6.6	60.0	45.2	16.8	28.4
7.0	65.0	41.0	14.1	26.9
7.7	70.0	37.8	11.7	26.1
8.4	75.0	34.3	9.3	25.0
9.5	80.0	29.5	7.3	22.2
10.9	85.0	24.0	5.4	18.6
12.8	90.0	17.5	3.4	14.1
15.6	95.0	10.0	1.6	8.4

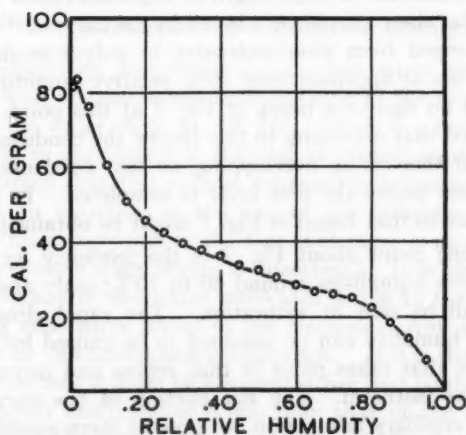


FIG. 7. Excess of net heat of adsorption over free energy.

There is one interesting point to consider in connection with the free energy. According to the expression $\frac{RT}{M} \log \frac{p_s}{p}$ the free energy should be infinite when the equilibrium pressure p approaches zero, and consequently the heat of adsorption should also become infinite. This does not seem to be borne out by any of the experimental work. In particular the experiments of Neale and Stringfellow (13), which were carried out at moisture contents as low as 0.00012 gm. per gm. of adsorbent indicate that there is no appreciable change in the heat of adsorption when the moisture content varies from 0.001 to 0.00012 gm. per gm. of adsorbent. The lowest of these moisture contents corresponds to a relative humidity of 0.006% and at this point the free energy would be 313 cal. per gram. Since Neale and Stringfellow found the net heat of adsorption to be only 289 cal. it appears that our relation derived above cannot hold in this region unless the experimental work is in error; this seems very unlikely. However, there is no reason to doubt the validity of our results at higher pressures and we shall consider that Fig. 7 gives a measure of the difference in internal energy between adsorbed moisture and liquid water until very low relative humidities are reached.

Fig. 7 then may be considered as indicating the state of the water vapour adsorbed on the cellulose surface. It shows by how much the energy of binding of the water molecule to the cellulose crystal is greater than the force of attraction between a water molecule and a free water surface. The first point of interest is to note that the molecule is more strongly attracted at low vapour pressures. The first atoms are either adsorbed on sites on the surface where the attractive force is greater than on the rest of the surface or the adsorbed atoms exert a repulsive force on one another so that as more atoms are adsorbed the attracting forces become smaller. This is explained on Brunauer, Emmett, and Teller's theory by assuming that as the number of adsorbed layers increase, the attracting force becomes less. However, according to this theory, a number of steps might be expected rather than a smooth curve. In particular there should be a break in the curve at the point where the adsorption changed from monomolecular to polymolecular adsorption. This transition occurs at approximately 20% relative humidity as shown in Fig. 1 and there is no sign of a break in Fig. 7 at this point. However, it must be remembered that according to this theory the condensation does not change sharply, but there is an overlapping, so that condensation begins in the second layer long before the first layer is completed. In this manner a smooth curve similar to that found in Fig. 7 might be obtained.

Another interesting point about Fig. 7 is the tendency for the curve to flatten out at relative humidities around 60 to 70%; only above that point does it start to fall to zero at saturation. The rapid drop between 80 and 100% relative humidity can be assumed to be caused by the change to capillary adsorption that takes place in that region and corresponds to the steep portion of the isotherm. The flat portion of the curve apparently indicates that were capillary adsorption not present there would be an energy

difference between adsorbed and free moisture even at saturation. As long as adsorption is molecular rather than capillary it can be assumed that there is an entropy difference between the adsorbed and liquid states.

It is difficult to account for a residual energy of this nature on the poly-molecular theory since according to this theory the heat of adsorption was assumed to approach the latent heat of condensation as the number of layers increased. On the basis of a monomolecular theory, however, such a residual energy would represent the energy of attraction of the surface minus the repulsive forces of the neighbouring adsorbed atoms.

It is interesting to note that the water initially adsorbed at low humidities has an excess energy of between 80 and 90 cal. This is in good agreement with the values obtained by evaluating $E_1 - E_L$ in the theory of Brunauer, Emmett, and Teller.

With respect to the heat of adsorption curve it is interesting to examine the explanation that Roberts (16) suggests for the curve found by Williams for the adsorption of sulphur dioxide on charcoal. As mentioned previously this curve is very similar in shape to that obtained for adsorption of water on cellulose. Roberts assumes that the adsorption is monomolecular and that the shape of the heat of adsorption curve can be attributed to the fact that the interaction between adsorbed molecules arises partly from van der Waals' attractive forces and partly from repulsions between permanent or induced dipoles. On page 101 of his book, Roberts gives curves showing how these two types of forces would vary with the fraction of surface covered, and by adding the two effects he obtains a curve that has the general features of the sulphur dioxide adsorption curve of Williams. Roberts assumes that the initial rapid drop found with such heat of adsorption curves "is presumably due to adsorption in crevices where an adsorbed atom is influenced by an abnormally high number of atoms of the solid."

The Problem of the Adsorption Compression

It is an established experimental fact that when water is adsorbed on cellulose the final volume is less than the sum of the original volumes of the cellulose and the water (8, 9, 11, 19, 21). There is a contraction in the total volume similar to that found in the case of certain aqueous solutions. It is generally assumed that this volume contraction is confined to the water and that there is no variation in the size of the cellulose crystals. (There is evidence for this assumption in the fact that there is no change in the X-ray diagrams of cellulose when water is adsorbed.) It is also assumed that the decrease in the size of the water molecules is due to the compression caused by the strong adsorptive forces of the cellulose. Any theory of adsorption must account for this adsorption compression. If it is the result of the strong attractive forces then it must be assumed either that (i) the length of the bond between the water and cellulose is less than that of the bond between water and water, or (ii) the water molecules are packed more closely on the surface

of the cellulose than they are in the natural state. It will be shown that the second of these hypotheses seems to offer an adequate explanation and gives a satisfactory picture of the phenomenon.

When the specific volume of cotton cellulose is determined by density measurements in helium, a value of 0.642 cc. is obtained, while similar measurements in water yield a value of 0.621 cc. (8, 9). There is thus a difference of 0.021 cc. in the apparent specific volume in the two cases. Similar measurements for white spruce wood substance given by Stamm (18) are 0.685 and 0.654 in helium and water, respectively. This represents a contraction of 0.031 cc. These facts are explained by assuming that helium is negligibly adsorbed so that the helium value represents the true volume of the cellulose and the smaller volume obtained with water is the result of the fact that adsorbed water does not occupy its ordinary volume.

Measurements are available giving this contraction in volume as a function of the moisture content of the cellulose. Thus J. R. Katz (11) gives the volume contraction when 1 gm. of wood fibre adsorbs $\frac{x}{m}$ grams of water. (His results are the mean values taken from measurements of H. Volbehr.) Filby and Maass (9) have calculated the apparent density of water adsorbed on cotton cellulose as a function of the adsorbed mass, and A. J. Stamm (18) has made similar calculations for white spruce wood substance. In order to compare these results we shall put them all in the form given by Katz, i.e., the total volume contraction when 1 gm. of dry adsorbent adsorbs $\frac{x}{m}$ grams of water. The results of Filby and Maass can be put in this form by plotting the specific volume of the water adsorbed at the different moisture contents and integrating graphically. The volume contraction can then be easily obtained by subtracting the resulting values from the volume that the water would occupy if the density had been unity. Stamm gives his results as the average density of adsorbed water at each moisture content. It is possible therefore to determine the average specific volume of the water at the different moisture contents and by subtraction to obtain the average contraction in volume. Multiplying this contraction by the corresponding moisture content gives the integral contraction at that moisture content. The results from the measurements are reproduced in Fig. 8.

It is to be noticed that there is fair agreement between the results of Filby and Maass and those of Katz, but that Stamm's measurements are considerably less. This might be caused by the difference in the materials used, as it is hardly to be expected that the spruce wood used by Stamm would give the same results as the cotton cellulose used by Filby and Maass or the "veränderte holzfaser" used by Katz. It is, however, surprising that Katz's measurements agree with those of Filby and Maass rather than with Stamm's.

There is one further point to be observed in connection with the measurements. Filby and Maass, and Katz, find the total contraction when the substance is saturated to be 0.045 cc., while Stamm finds it to be about 0.31 cc.

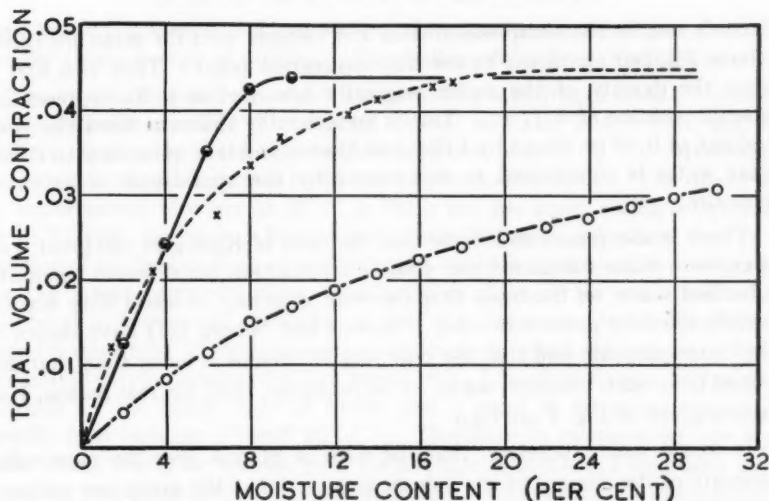


FIG. 8. Total volume contraction in cubic centimetres per gram of adsorbent. ●, Filby and Maass. X, Kats. ○, Stamm.

This contraction should check with the differences in the specific volumes found by measurements in helium and water. As mentioned previously the contraction found in that way was 0.021 cc. for cotton and 0.031 cc. for white spruce wood. Stamm's value does agree with the latter but since he used this value originally in calculating his densities no added significance can be obtained from the coincidence. The value of 0.045 cc. however does not agree with either the results from cotton or those from spruce wood. This is sufficient to cause considerable doubt regarding the accuracy of these measurements and indicates the need for more work of this nature.

The values that Filby and Maass obtain for the densities of the water originally adsorbed by the cellulose are very interesting if reliance can be placed in them. Below 3% moisture content they find a uniform density of 2.6 gm. per cc. At higher moisture contents the apparent density becomes less, until above 9% moisture content the water adsorbed appears to have its normal density.

These figures are surprising. A density of 2.6 represents a specific volume of 0.38 cc., and to compress water to this extent by means of an externally applied force would require a pressure of several hundred thousand atmospheres. If the bond between the cellulose and the water is so much stronger than the bond in liquid water a heat of adsorption of a completely different order of magnitude from that of the latent heat of evaporation should be expected. It should rather approximate to the heat of formation of a water molecule from hydrogen and oxygen.

The work of Stamm and Seborg (21) has thrown considerable doubt on these measurements of Filby and Maass. They find that contrary to the

latter's results the compression does not become zero for moisture contents above 9% but continues to the fibre-saturation point. They also find (18) that the density of the water originally adsorbed is 1.30, representing a specific volume of 0.77 cc. This is considerably different from the specific volume of 0.38 cc. found by Filby and Maass, and it is quite easy to conceive that water is compressed to this extent by the application of an external pressure.

There is also reason to believe that the data of Katz give too great a compression. Katz calculated the volume contraction for different amounts of adsorbed water on the basis that the void structure of wood fibre was completely filled by petroleum ether. Stamm and Seborg (21) have shown that this is not the case and that the true specific volume is lower than that determined from such measurements. It is probable, that, for this reason, Katz's results given in Fig. 8 are high.

It would seem, therefore, that the data of Stamm give the most reliable estimate of the amount of the volume contraction. We must now endeavour to find a reasonable explanation of how such a compression can occur.

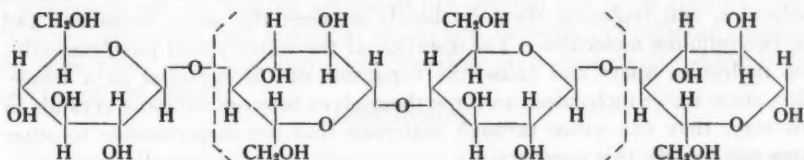
According to the picture of water put forward by Bernal and Fowler (4) the water molecules in ice are arranged in a somewhat distorted tetrahedral system. Each oxygen atom is connected with four other oxygen atoms and the hydrogen atoms lie on the lines joining the oxygen atoms, but are not midway between them. Each oxygen atom has two hydrogen atoms at a distance of 0.99 Å, corresponding to the gaseous molecule where the distance is 0.96 Å, and two other hydrogen atoms at a distance of 1.77 Å. Thus the distance between the oxygen atoms is 2.76 Å. Bernal and Fowler found that this structure also prevails to a certain extent in liquid water, but in this case at room temperatures it is continually alternating with a quartz type of structure. This conception of water represents a very open structure, for were the water molecules having a diameter of 2.76 Å arranged in the most compact configuration possible a structure would be obtained with a density of about 1.8, i.e., it would be nearly twice as dense as water.

Thus there is much open space in liquid water and by a rearrangement of the molecules it would be easily possible to account for a density of 1.30. In fact, a density of this order has been found for certain types of ice. Bernal and Fowler, quoting from the data of Bridgman, show that ice VI, which exists at pressures above 6000 atm., has a specific volume of 0.76 cc. This corresponds very closely to the density observed by Stamm for the water initially adsorbed on cellulose. There would be then no difficulty from molecular considerations in accounting for the decreased volume of this adsorbed water. It must be remembered, however, that at low moisture contents the number of molecules is so small that the monomolecular layer is far from complete and any comparison with the structure of ice may be misleading. The problem is rather to attach the water molecules to the surface of the cellulose in such a way that they will occupy less volume than

they would if attached to a free water surface, and at the same time to account for the excess energy of binding. We shall consider how this might occur.

The oxygen molecules in water are united by a hydrogen bond. According to Pauling the strength of the bond O-H-O in water is 4.5 kcal. per mole and the distance between the oxygen molecules is 2.76 Å. In vaporizing ice it is necessary to break two hydrogen bonds per molecule. The latent heat of vaporization of water at 20° C. is 584.9 cal. per gram, which is equivalent to 10.53 kcal. per mole. Bernal and Fowler (4) have calculated that in the melting of ice the breaking of one-eighth of the hydrogen bonds would account for the latent heat of fusion. Similarly, to account for the specific heat, one bond in four would be broken at 100° C. So it may be assumed that in liquid water at 20° C. there is an open structure in which the oxygen molecules are united on the average by 3.4 bonds (i.e., 1 bond in 8 must be broken to account for the latent heat of fusion and 1 bond in 40 to account for the specific heat between 0° and 20° C.). Therefore in evaporating one water molecule it would be necessary on the average to break 1.7 hydrogen bonds, since the bonds are common to two molecules. To evaporate a gram-molecule of water would require $4.5 \times 1.7 = 7.65$ kcal. per gm. simply to disrupt the hydrogen bonds. (Presumably the $10.53 - 7.65 = 2.88$ kcal. per gram-mole that remain in the heat of evaporation are due to van der Waals' and dipole forces.)

On the other hand, let us examine the possible means by which the water molecule may be attached to the cellulose molecule. Cellulose has the formula $(C_6H_{10}O_5)_n$, and the unit arrangement may be represented as follows:



These units are united in long chains of several hundred to form the cellulose molecules, and in turn these molecules are joined together to form the cellulose fibres. Presumably the link between the different molecules is made through a hydrogen bond, the oxygens in two of the side chains being joined through a hydrogen atom.

It is justifiable to assume that the water molecule is adsorbed on the cellulose molecule by means of two hydrogen bonds connecting the oxygen in the water molecule to two of the oxygen atoms in the side chains on the cellulose molecule. This water would thus be linked with two hydrogen bonds per molecule instead of the 1.7 bonds as calculated for liquid water. This represents an energy of 1.35 kcal. per mole or 75 cal. per gm. This value is of the same order as the excess that was found for the heat of adsorption in Fig. 5. It is very probable also that the hydrogen bonds in this case will have an energy greater than 4.5 kcal. per mole, as the configuration of the

oxygen molecules affects the strength of the bond. Thus, in the aliphatic alcohols the hydrogen bond has an energy of 6.2 kcal. per mole. It seems therefore that a mechanism of this nature is quite adequate to explain the heat of adsorption found for the water originally adsorbed on the cellulose.

There are two other observational facts that will help us to form a complete picture of the adsorption phenomenon. In the first place it is well known that when wood or other cellulosic substance adsorbs water, the adsorption is accompanied by an expansion in the physical dimensions of the material, that is to say, swelling takes place. Second, water vapour has been found to diffuse much more easily than other gases through some materials. Thus rubber is over 50 times more permeable to water vapour than to hydrogen, and cellulose products themselves, such as paper or wood, transmit water much more quickly than air. This indicates that water molecules can move through these materials with a greater ease than would be expected from a consideration of the relative sizes of the molecules. In other words there appear to be very good grounds for believing that water molecules can enter small cracks or crevices that much smaller atoms cannot.

These two facts fit together very well to give an idea of what happens to the water molecule when it is adsorbed. It has been shown by X-ray analysis that cellulose swollen in water has the same crystal dimensions as normal cellulose. Hence the swelling must take place between the crystals. It has been pointed out here that the cellulose crystals are most probably joined together by hydrogen bonds. If this is so, the water molecules might enter between the crystals, breaking the hydrogen bonds joining the cellulose molecules, and replacing them by bonds between the water molecules and the two cellulose molecules. The insertion of the water would push the cellulose molecules apart and cause the expansion of the material as a whole. Also, since water molecules can force themselves between cellulose crystals in this way, they can move through materials that are impermeable to other gases not having this property.

The fact that the water molecule is able to force itself between cellulose crystals where other smaller molecules cannot enter is sufficient in itself to explain the volume contraction found when moisture is adsorbed by these substances. For in the experimental work that shows this contraction the assumption is made that the true volume of the cellulose is given by density measurements in helium. If however the water molecules can penetrate between the crystals into void spaces that are closed to helium then the true volume of the cellulose would not be given by the helium measurements. However, a conception of this nature is not satisfactory as an explanation of the volume compression occurring in certain aqueous solutions, such as sulphuric acid, and since the dilution of solutions is very similar thermodynamically to adsorption it is probable that the adsorbed water actually is arranged in a much closer structure in the adsorbed state than in the free liquid. In making the density measurements in water, the volume of the water adsorbed is lost, since it has entered spaces within the cellulose structure

that were not available to the helium atoms. If it were not for the fact that these molecules of adsorbed water push the cellulose fibres apart and cause swelling, there would be no evidence on the basis of the usual type of measurements that they occupied any volume at all. The volume that is actually measured as occupied by the adsorbed water is the expansion of the cellulose structure. On the basis of this conception the expansion would be equal to the volume occupied by the adsorbed water. Unfortunately, however, because of the fact that cellulose has a sponge-like structure with internal air spaces, a measure of the expansion of the external physical dimensions does not reveal the total volume expansion since some of this expansion takes place in the internal air spaces. However, a qualitative relation might be expected between the volume occupied by the adsorbed water and the expansion. Collins (7) did find such a relation from the variation with temperature of the swelling of cotton hairs and the volume contraction as measured by Davidson (8), but he concludes that his measurements were "not capable of yielding any quantitative information as to the variation or significance of the value of the apparent specific volume of the adsorbed water." Thus, while there is no direct support for such a hypothesis, the available evidence does not seem to contradict it.

The observations made above naturally do not refer to capillary-adsorbed water since this water is obviously condensing in capillaries, which are accessible to helium gas. In that case there is no reason to believe that the volume occupied by water is other than that which one should expect it to occupy under such conditions. However, it must be realized that the different types of adsorption are not sharply separated but overlap and occur concurrently. Capillary adsorption and molecular adsorption between the cellulose crystals will take place simultaneously, and therefore it is exceedingly difficult to disentangle the effects.

Conclusion

The above discussion of the adsorption of water vapour by cellulose presents the following picture of the phenomenon:

1. The adsorption isotherm may be explained for a small region at low humidities by adsorption in a monomolecular layer obeying Langmuir's equation. In the region between 20 and 80% relative humidity the adsorption agrees with the polymolecular theory of Brunauer, Emmett, and Teller but a monomolecular theory assuming a decrease in attraction as the number of adsorbed molecules increases is not thereby excluded. In the region between 80% relative humidity and saturation it seems necessary to assume that capillary adsorption is predominant.

2. The heats of adsorption taken from various sources are found to give fairly consistent values, and when these heats of adsorption are plotted against the relative humidity the results obtained with cotton do not differ appreciably with those obtained with wood. When the heats of adsorption are compared with the free energy it is found that an extra energy term is

involved in the heat of adsorption, and this is assumed to be caused by an increased internal energy in the adsorbed state.

3. The study of the possible ways in which the water molecules may be attached to the cellulose crystals has shown that the increased energy of adsorption may be accounted for by assuming that the water molecules are attached to the cellulose by two hydrogen bonds. By considering the three dimensional arrangement of the cellulose molecule it should be possible to account for the contraction in volume that occurs during adsorption, and also to relate this to the swelling of the cellulose.

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STUDIES ON REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES

LXVII. SYNTHESIS OF METHYLATED GLUCOSE DERIVATIVES¹

BY TAYLOR H. EVANS², IRVING LEVI³, W. LINCOLN HAWKINS⁴,
AND HAROLD HIBBERT⁵

Abstract

The Haworth methylation technique has been modified to provide improved methods of synthesis of 2,3-dimethyl- α - and β -methyl glucosides and 2,3,4,6-tetramethyl glucose from glucose, and of 2,3,4-trimethyl methyl glucosides from levoglucosan. A new crystalline derivative of 2,3-dimethyl glucose, the gluconophenylhydrazide, has been prepared and found to serve as a valuable identification medium.

Introduction

Various derivatives of 2,3-dimethyl glucose, 2,3,4-trimethyl glucose, and 2,3,4,6-tetramethyl glucose were required in studies on the structures of Dextran I (17) and II (1), and it was found that, although many of these substances had been prepared previously, either the details of the procedures had been reported incompletely in the literature or the yields were low. These methylated glucose derivatives have now been synthesized by methods capable of giving higher reproducible yields and applicable not only to glucose but also to rarer carbohydrates.

Throughout these preparations, hydrolyses of the various intermediates were carried out using dilute sulphuric acid rather than dilute hydrochloric acid, the conventional hydrolytic agent, since sulphuric acid is easily removed as barium sulphate. Also Haworth methylation (in an atmosphere of nitrogen) was substituted for the laborious Purdie technique.

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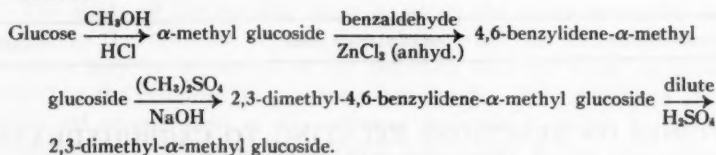
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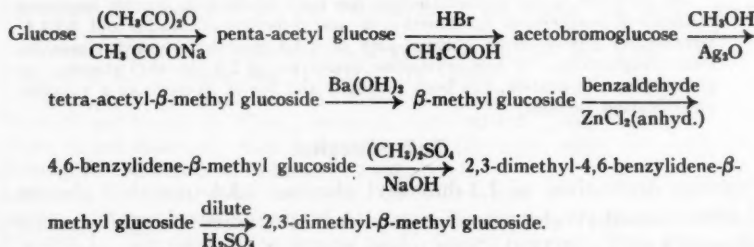
2,3-Dimethyl- α -methyl glucoside (14) was prepared by the following series of reactions:



This procedure gives almost quantitative yields for amounts of material varying from 5 to 50 gm.

The benzylidene group is stable under the conditions of the Haworth methylation used, as shown by the high yield of product isolated.

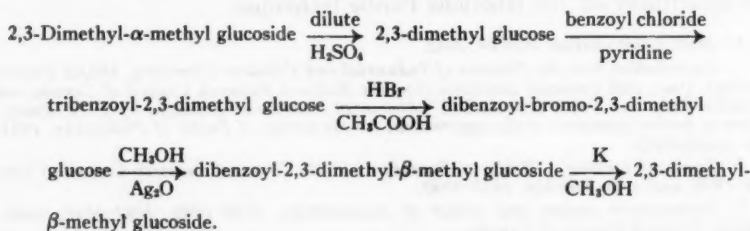
2,3-Dimethyl- β -methyl glucoside was prepared by two different methods. The first may be summarized as follows:



The final product in this case was crystalline, in contrast with the liquid product obtained by Oldham's method (20) using dilute hydrochloric acid as the hydrolytic agent.

Improved yields of tetra-acetyl- β -methyl glucoside were obtained by a modification of the Königs-Knorr reaction introduced by Reynolds and Evans (22). This included the addition of activated Drierite (16) as desiccant, and of iodine to catalyze the elimination of water.

The second method of preparation of 2,3-dimethyl- β -methyl glucoside was adapted from Oldham's (19) procedure and may be summarized as follows:

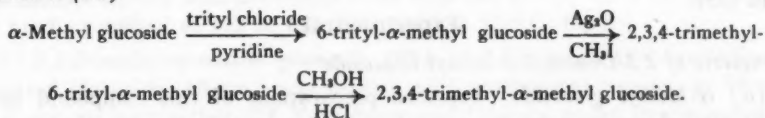


Drierite and iodine (16, 22) were also added to the Königs-Knorr reaction mixture in this synthesis.

A new crystalline derivative of 2,3-dimethyl glucose, viz., 2,3-dimethyl gluconophenylhydrazide was prepared. 2,3-Dimethyl glucose was oxidized to the corresponding dimethyl gluconic acid by the method of Hudson and Isbell (12); the product was isolated by a slightly different procedure as a syrup (84% yield) and was converted to the crystalline phenylhydrazide in 80% yield.

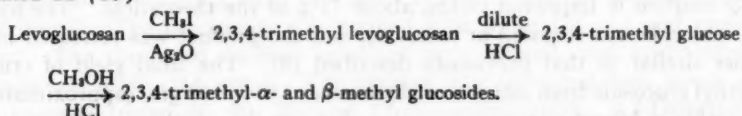
There are two principal methods described in the literature for the preparation of 2,3,4-trimethyl methyl glucosides.

Method I (23)



The yields obtained by this procedure are generally low, particularly in the first step.

Method II (13)



A modification of the latter procedure was used to synthesize 2,3,4-trimethyl- α - and β -methyl glucosides. In preliminary experiments, lower temperatures and shorter reaction periods were employed (cf. (26)) in the Haworth methylation of levogluconan, but these led to low yields of incompletely methylated products. The normal procedure for Haworth methylation was therefore used and the 1,6-oxygen bridge in levogluconan was found to be quite stable under these conditions. Trimethyl levogluconan was hydrolysed to trimethyl glucose by means of dilute sulphuric acid.

The preparation of 2,3,4,6-tetramethyl glucose as described in the literature (6, 7, 8) is neither a quantitative nor a one-step procedure. The methylation of glucose as given by Haworth (6, 7, 8) results in low yields of partially methylated glucose. One methylation of glucose or α -methyl glucoside using the authors' modified procedure yielded a mixture of tetra-, tri-, and dimethyl methyl glucosides, separable by fractional distillation. Two such successive methylations of α -methyl glucoside gave a 91% yield of relatively pure 2,3,4,6-tetramethyl- α -methyl glucoside. This yield is considerably higher than those obtained previously (10, 25), indicating no appreciable degradation of the partially methylated glucoses during the Haworth methylation in a nitrogen atmosphere. Of the other reported methods, one (25) involves a Haworth methylation at the boiling point of carbon tetrachloride, used as solvent, while in another (10) a modified Haworth methylation is followed by Muskat methylation. The necessity for long reaction periods is evident.

It was found that the simplest method of extracting the methylated carbohydrates of relatively high methoxyl content (e.g., tetra- or trimethyl) present in the Haworth methylation reaction mixture was to reflux the latter with chloroform, and separate the chloroform layer. An additional advantage of this method was the fact that higher methylated products were found preferentially soluble in chloroform (cf. (18)), while those of lower methoxyl content remained in the water layer, which could be concentrated and remethylated.

Hydrolysis of 2,3,4,6-tetramethyl- α -methyl glucoside was carried out, with sulphuric rather than dilute hydrochloric acid, or steam and hydrochloric acid (25).

Experimental

*Synthesis of 2,3-Dimethyl- α -methyl Glucoside**

(a) *α -Methyl glucoside.* Previous preparations of this compound have been carried out by refluxing a glucose solution in anhydrous methanol containing 3% hydrogen chloride for only 4½ hr. (21) or by refluxing with 0.25% hydrogen chloride in methanol for 144 hr. (9). These procedures were modified, and refluxing for a total of 40 hr. with a hydrogen chloride concentration of 3% resulted in improved yields, about 75% of the theoretical. The hydrogen chloride was renewed at intervals, and the product was retreated in a manner similar to that previously described (9). The total yield of crude α -methyl glucoside from 200 gm. of glucose was 150 to 160 gm. (approximately 70% yield). After two recrystallizations from methanol, this product melted at 165 to 165.5° C.† (165 to 166° C. (21)); yield, 100 to 110 gm.

(b) *4,6-Benzylidene- α -methyl glucoside (5, 14).* Merck benzaldehyde was redistilled in an atmosphere of nitrogen. B.p. 179.5° C. Dry finely ground α -methyl glucoside (25 gm., m.p. 165 to 166° C.), freshly distilled benzaldehyde (70 gm.), and finely ground fused zinc chloride (20 gm.) were shaken for six hours at room temperature. After standing 12 hr. at 0° C., the solution was poured in a fine stream into ice-water (400 cc.). The benzylidene compound separated as a fine white powder, which was filtered and washed with ice-water. The precipitate was then shaken with 10% sodium bisulphite solution (five 100 cc. portions) to free it from excess benzaldehyde, the wash liquors being decanted through the Büchner funnel. The benzylidene compound in the funnel was washed with a cold saturated solution of sodium bicarbonate (300 cc.), and ice-water (400 cc.), and finally with petroleum ether (b.p. 30 to 50° C.) to remove last traces of benzaldehyde. The yield of crude product was 28.5 gm. (78%). The 4,6-benzylidene- α -methyl glucoside (after one recrystallization from water) melted at 163 to 164° C. (161 to 162° C. (5)).

(c) *2,3-Dimethyl-4,6-benzylidene- α -methyl glucoside (5, 14).* Crude 4,6-benzylidene- α -methyl glucoside, as obtained above, can be methylated in good

* The procedures described for the synthesis of this compound are slight modifications of unpublished methods developed by previous workers in these laboratories, notably Dr. E. C. Fairhead and Dr. H. P. Godard.

† Melting points are uncorrected.

yield without a preliminary recrystallization. 4,6-Benzylidene- α -methyl glucoside (12.5 gm.) was dissolved in acetone (75 cc.) at 40° C. and placed in a 500 cc. three-necked flask equipped with a stirrer and two burettes. Dimethyl sulphate (25 cc.) and 30% aqueous sodium hydroxide (75 cc.) were added in tenth portions at 10-min. intervals with stirring. After an additional hour's stirring, hot water (100 cc.) was added, and the solution was heated to 100° C. to destroy sodium methyl sulphate. The reaction mixture was cooled, and the methylated product filtered off. The yield of crude material was 12.4 gm. (90%). After one crystallization (88% yield, neglecting possible recovery from mother liquor) from petroleum ether (b.p. 100 to 110° C., 8 cc. per gm.), this product melted at 122 to 122.5° C. (122 to 123° C. (5)).

(d) *2,3-Dimethyl- α -methyl glucoside (14)*. 2,3-Dimethyl-4,6-benzylidene- α -methyl glucoside (10 gm.) was heated, with mechanical stirring, at 85 to 90° C. for one hour with 0.275 *N* sulphuric acid (100 cc.) under an atmosphere of nitrogen. The cooled reaction mixture was extracted five times with ether, using 20 cc. each time. The combined ether solutions were back-extracted with water (20 cc.). The aqueous solution was neutralized to Congo red with barium carbonate ground to a paste in water, and the barium sulphate centrifuged. The precipitate was washed with water (25 cc.) and recentrifuged. The combined aqueous solutions were filtered, and evaporated to dryness at 40° C. (15 mm.). The residue was extracted four times with hot benzene (using 40, 30, 20, and 10 cc. respectively). 2,3-Dimethyl- α -methyl glucoside crystallized out when the benzene solution was cooled. After one recrystallization from the same solvent, the product melted at 81.5 to 83° C.; yield, 6.5 gm. (90%).

2,3-Dimethyl-6-trityl- α -methyl glucoside was prepared according to a previously reported method (4).

2,3-Dimethyl Gluconophenylhydrazide

(a) *2,3-Dimethyl gluconic acid*. 2,3-Dimethyl glucose was oxidized with aqueous bromine in the presence of barium benzoate (12). The aqueous solution was evaporated to dryness at 70° C. (20 mm.) after removal of inorganic salts and benzoic acid, and the pale yellow residual syrup extracted with hot anhydrous dioxane. A pale yellow syrup (OCH_3 , 27.4%; theoretical for $\text{C}_6\text{H}_{10}\text{O}_6(\text{OCH}_3)_2$, 27.7%), non-reducing to Fehling's solution, was obtained after evaporation of the dioxane. Yield, 84%.

(b) *2,3-Dimethyl gluconophenylhydrazide*. 2,3-Dimethyl gluconic acid (0.80 gm.) was dissolved in anhydrous ether (50 cc.) by refluxing for three hours. A fine white precipitate formed at once on the addition of freshly distilled phenylhydrazine (2.0 gm.), and after seven hours' refluxing it was removed by filtration. Additional material was recovered from the filtrate by further treatment with phenylhydrazine and concentration of the reaction mixture. The total yield of crude material was 1.08 gm. (96% of theoretical), which, after two recrystallizations from ethanol, separated as fine, short, white needles, m.p. 166.5 to 167° C. Yield, 0.9 gm. Found: C, 53.3; H, 7.1;

N, 9.3; OCH_3 , 19.6%. Calc. for $\text{C}_{14}\text{H}_{22}\text{O}_6\text{N}_2$: C, 53.5; H, 7.0; N, 8.9; OCH_3 , 19.7%.

Synthesis of 2,3-Dimethyl- β -methyl Glucoside

Method No. 1

β -Methyl glucoside was first prepared by a four-step procedure.

(a) *Penta-acetyl glucose* was prepared as previously described (2). The crude product was recrystallized from five parts of ethanol; yield, 67%. After two further recrystallizations, the pure product melted at 130 to 131° C. Various melting points have been reported (24) in the literature by different investigators, e.g., 132° C., 134 to 135° C.

(b) *Acetobromoglucose* was prepared as described previously (2). Recrystallization was effected by use of an ether-petroleum-ether mixture and a purer product was obtained in higher yield (73%) than by use of amyl alcohol (2). M.p. 87.5 to 88.5° C. (88° C. (15)).

In this preparation, the time required to isolate the product after dilution of the reaction mixture with water must be minimized as much as possible in order to obtain satisfactory yields. The pure product decomposes readily unless stored over phosphorus pentoxide in a desiccator.

(c) *Tetra-acetyl- β -methyl glucoside* was prepared by a Königs-Knorr reaction of methanol and acetobromoglucose in the presence of silver oxide following the method of Reynolds and Evans (22) for the preparation of α - and β -gentiobiose octa-acetates. The product was recrystallized from methanol; m.p. 101 to 102.5° C. (uncorrected); yield, 76%. Hudson and Dale (11) report a corrected m.p. of 104 to 105° C. after several recrystallizations.

(d) *β -Methyl glucoside* was obtained from tetra-acetyl- β -methyl glucoside in 93% yield by the method used for the preparation of α -methyl glucoside (3). The product was recrystallized from methanol by the addition of ether; m.p. 107.5 to 109° C. (110° C. (21)).

The preparation of 2,3-dimethyl- β -methyl glucoside from β -methyl glucoside followed, in general, the procedure outlined above for that of 2,3-dimethyl- α -methyl glucoside from α -methyl glucoside.

(e) Crude 4,6-benzylidene- β -methyl glucoside (5) was obtained as a gummy product. After trituration in a mortar with sodium bisulphite solution, the yield of crude material was 67%. Recrystallized from water, the product melted at 199 to 201° C. (194° C. and 205° C. (5)).

(f) 2,3-Dimethyl-4,6-benzylidene- β -methyl glucoside. 4,6-Benzylidene- β -methyl glucoside was not sufficiently soluble in acetone at 40° C. to allow of methylation with dimethyl sulphate and sodium hydroxide; dioxane was therefore used as a solvent for the Haworth methylation. The yield of crude material (one experiment only) was about 50%. Considerable losses resulted on recrystallization from petroleum ether (b.p. 100 to 110° C.) and from ethanol; m.p. 132 to 133° C. (132 to 135° C. (20)).

(g) *2,3-Dimethyl- β -methyl glucoside* (19, 20). 2,3-Dimethyl-4,6-benzylidene- β -methyl glucoside (0.9 gm., m.p. 132 to 133° C.), ethanol (50 cc.) and 0.27 *N* sulphuric acid (20 cc.) were heated at 60 to 65° C. for one and one-half hours in an atmosphere of nitrogen. The product was isolated by the method used for the α -isomer. It could not be crystallized from petroleum ether (b.p. 60 to 70° C.) nor from chloroform on the addition of petroleum ether (b.p. 30 to 50° C.). Yield, 0.5 gm. (78%); OCH_3 , 38.9%. Distillation of the oil in a Späth bulb (bath temperature 125° C./0.003 mm.) yielded a colourless oil; OCH_3 , 41.0% (theoretical, 41.9%). This material crystallized on standing; m.p. 60 to 61° C. (62 to 64° C. (19)).

Method No. 2

This was a modification of that of Oldham (19) discussed above.

(a) *2,3-Dimethyl glucose* (14). 2,3-Dimethyl- α -methyl glucoside (10 gm., m.p. 82 to 83° C.) was heated with normal sulphuric acid (400 cc.) in an atmosphere of nitrogen for 16 hr. in a water-bath at 100° C. The rotation was constant during the last two hours, and the reaction was adjudged complete. The product was isolated according to the procedure outlined for 2,3-dimethyl- α -methyl glucoside except that no preliminary ether extraction was necessary and methanol was substituted for benzene. Evaporation of the methanol yielded 9.2 gm. (quantitative); OCH_3 , 29.7% (theoretical, 29.8%).

(b) *Tribenzoyl-2,3-dimethyl glucose, dibenzoyl-2,3-dimethyl- β -methyl glucoside* and *2,3-dimethyl- β -methyl glucoside* were prepared according to Oldham's procedure (19), except that the improved Königs-Knorr technique (22) mentioned above was again used. After one recrystallization from carbon tetrachloride the 2,3-dimethyl- β -methyl glucoside melted at 60 to 62° C.

Preparation of 2,3,4-Trimethyl Glucose

(a) *2,3,4-Trimethyl Levoglucosan* (13)

Levoglucosan (10 gm., m.p. 177° C.) was dissolved in water, and the solution stirred in an atmosphere of nitrogen. Dimethyl sulphate (10 cc.) was added immediately, and sodium hydroxide (20 cc. of a solution of 100 gm. in 175 cc. water) added dropwise during two hours. Dimethyl sulphate and sodium hydroxide (20 cc. and 40 cc. respectively) were added dropwise and in approximately equivalent amounts during 1½ hr. The temperature was slowly raised to 60° C. during the next two hours, then dimethyl sulphate (10 cc.) added slowly. The temperature was kept at 60° C. for four hours, and the reaction mixture stirred at 50° C. for 12 hr. Following this it was about half neutralized with 50% sulphuric acid, heated at 100° C. for one-half hour, cooled below 20° C. and rendered slightly alkaline to phenolphthalein by the addition of 50% sulphuric acid. The reaction mixture was exhaustively extracted by refluxing with several successive portions of chloroform (e.g., 100, 75, 50, 50, and 50 cc.). The combined chloroform extracts were dried and evaporated under reduced pressure; yield, 10 gm. (A). The aqueous mother liquor was cooled at -15° C., sodium sulphate removed and the

solution concentrated (B). The methylated levoglucosan (A) was not completely crystalline, since it was not fully methylated. After two recrystallizations from ether, the product melted at 59° C. Material recovered from the mother liquors was added to the concentrated aqueous methylation solution (B) and both were again methylated using dimethyl sulphate and sodium hydroxide as described above. The total yield of product from all these operations was 10 gm. approximately (80%). On recrystallization from ether, it melted at 59° C.; yield, 8 gm.

(b) *2,3,4-Trimethyl Glucose*

Trimethyl levoglucosan (5 gm., m.p. 59° C.) in 3.6% sulphuric acid (100 cc.) was heated at 100° C. for 17 hr. (constant rotation). The product was isolated according to the procedure outlined for 2,3-dimethyl glucose, except that acetone replaced methanol as solvent. Yield (light-yellow oil), 5.1 gm. (96%): OCH_3 , 41.6%; theoretical, 41.9%.

Extensive decomposition of 2,3,4-trimethyl glucose resulted when this compound was distilled (even in an atmosphere of nitrogen) at temperatures and pressures lower than those used by Irvine and Oldham (13). However, since the 2,3,4-trimethyl glucose prepared by the method outlined above is relatively pure it was employed without further purification.

(c) *2,3,4-Trimethyl- α - and β -Methyl Glucosides from 2,3,4-Trimethyl Glucose*

2,3,4-Trimethyl glucose (5.0 gm.) dissolved in anhydrous methanol (140 gm.) containing anhydrous hydrogen chloride (4 gm.) was refluxed for 17 hr. at which time the solution was no longer reducing to Fehling's solution. Addition of silver carbonate (5 gm.) rendered the solution slightly alkaline to Congo red. The mixed glucosides were separated from silver salts and methanol in the usual manner; yield, 4.9 gm. (92%).

This product was fractionally distilled, in an atmosphere of nitrogen, through a Widmer column, bath temperature 125 to 185° C. (0.07 mm.); residue, less than 5%. The first portion of the distillate was predominantly crystalline 2,3,4-trimethyl- β -methyl glucoside. When crystallized from petroleum ether (b.p. 30 to 50° C.) containing about 5% ether, this melted at 93 to 94° C. (94° C. (4)). The remainder of the distillate was largely 2,3,4-trimethyl- α -methyl glucoside: OCH_3 , 52.1%; theoretical, 52.6%.

Preparation of 2,3,4,6-Tetramethyl Glucose

(a) *2,3,4,6-Tetramethyl- α -methyl Glucoside*

This was prepared by Haworth methylation of α -methyl glucoside following the procedure given above for the methylation of levoglucosan. The product was recovered by chloroform extraction (as described above) in such amount that remethylation of the mother liquor was not advantageous. Yield of

crude product, 35.8 gm. from 30 gm. α -methyl glucoside; n_D^{22} , 1.4525 (tetramethyl α -methyl glucoside, n_D^{20} , 1.4460 (25); trimethyl methyl glucoside, 1.4578).

The crude product was remethylated; yield, 35.3 gm. (91%). n_D^{22} , 1.4458. This material was fractionally distilled through a Widmer column, and 32.1 gm. obtained; b.p. 91.5 to 93° C. (0.5 to 0.6 mm.) (bath temperature, 130 to 140° C.); OCH_3 , 59.8%. Redistillation at 90.5 to 93° C. (0.5 to 0.6 mm.) (bath temperature, 120° C.) yielded 31.8 gm. n_D^{22} , 1.4453; OCH_3 , 61.3%, theoretical 62.0%.

Two Haworth methylations of glucose following the same procedure gave high yields of tetramethyl methyl glucosides when the methylations were carried out in an atmosphere of nitrogen and at a lower preliminary temperature (20 to 30° C. for the first three hours during which time too great an excess of sodium hydroxide was avoided). Under these conditions, the glucosidic hydroxyl is methylated before extensive decomposition occurs (8).

(b) 2,3,4,6-Tetramethyl Glucose

2,3,4,6-Tetramethyl- α -methyl glucoside (10 gm.) was hydrolysed at 100° C. with 5% sulphuric acid (200 cc.) until constant rotation was reached (about 12 hr.). The product was isolated as described above for 2,3-dimethyl glucose, ether being used as the final solvent. The product, partially crystalline, was dissolved in petroleum ether (b.p. 30 to 50° C.) containing 5 to 10% ether, from which a portion of the product crystallized. The non-crystalline material in the mother liquor was rehydrolysed, and recrystallized from the petroleum ether and ether mixture. The total yield of crystalline material was approximately 8 gm. (76%); OCH_3 , 52.4% (theoretical, 52.5%). After one additional recrystallization, the product melted at 90 to 91° C. (90 to 93° C. (25)).

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KINETICS OF THE ALKALINE HYDROLYSIS OF PROPIONITRILE¹

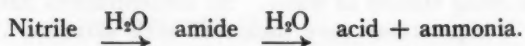
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Abstract

Some contradictory points recorded for the alkaline hydrolysis of nitriles have been clarified by a study of propionitrile hydrolysis in aqueous sodium hydroxide solutions of concentration 0.3 to 4 *N*. It has been shown that the rate of alkaline hydrolysis of propionitrile is given by the rate of formation of total ammonia and intermediate amide and not by that of ammonia alone. The relative rates of propionitrile and propionamide hydrolysis were found to be approximately 1 : 10 over the whole alkali concentration range. The bimolecular velocity constant is essentially independent of alkali concentration. An activation energy of 20,300 cal. was determined for the reaction in 0.65 *N* alkali.

Introduction

The hydrolysis of nitriles proceeds through the amide to yield the corresponding acid and ammonia:



The existing state of knowledge of the reaction in alkaline solutions is unsatisfactory. Both the relative rates of the consecutive reactions of simple aliphatic nitriles and amides (7, 10), and the occurrence of an induction period in the nitrile hydrolysis (10, 12), appear to be in doubt. With respect to the latter point, data on the alkaline hydrolysis of substituted acetonitriles (1, 2), of which those of the second paper only were accessible, have been stated to follow the bimolecular equation. However, since these velocity data refer usually to less than 5% reaction and display deviations in this range as high as 15% from the mean, this evidence appears unsatisfactory.

It has been found (8, 11) for the acid hydrolysis of nitriles, which has been studied in some detail, that the activation energy depends on acid concentration, and that the variation of rate with acid concentration could be related to the activation energy change. Existing studies of the effect of temperature on the rate of hydrolysis in alkaline solutions have been restricted to a range of only 7° C. for acetonitrile and propionitrile (10), and to a range of only 10° C. for certain substituted acetonitriles (1, 2), at one alkali concentration in each instance.

In view of the contradictory points mentioned above, it seemed of interest to investigate the alkaline hydrolysis of propionitrile, for which nitrile the acid studies were the most complete, and to examine the Arrhenius parameters over a range of alkali concentration. Owing to circumstances beyond control

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of the authors, the study had to be terminated before the Arrhenius parameters could be examined. It was uncertain when further work on the problem might be possible, and the results obtained to date are presented since they clarify to a large extent the controversial points.

Materials and Procedure

An aqueous, saturated solution of reagent grade sodium hydroxide was prepared, the carbonate precipitated, and the alkali standardized by means of constant boiling hydrochloric acid. Solutions of known strength were prepared by dilution. All solutions were protected from air.

Propionitrile was obtained commercially and fractionated to a constant boiling point. Aqueous solutions were prepared by direct weight, such that nitrile concentrations in the reaction mixtures were approximately 0.3 *N*.

Equal volumes of alkali and nitrile solutions were mixed at 0° C., and Pyrex tubes were filled, sealed, and immersed in thermostats regulated to 0.1° C. The volume change on mixing was determined with the aid of density-percentage data for sodium hydroxide in International Critical Tables, the nitrile solution being treated as water. All concentrations have been taken as at 25° C. Temperatures were measured with standard thermometers. An experimentally determined correction was made for the time required for solutions to warm to reaction temperature. From time to time, tubes were removed, quickly cooled, and analysed. It was found that the products of reaction exert a retarding effect, so that reaction was allowed to proceed to only about 60% completion.

In following the course of the reaction, analysis was made either for ammonia alone, or for total amide and ammonia by methods described earlier (11). No difficulty was experienced from loss of ammonia upon opening the tubes, at alkali concentrations below 2 *N*. At 4 *N*, the results tended to be erratic, although in the run at this concentration recorded below, which is a better one, the individual *k* values showed an average deviation from the mean of only 3%.

Results and Discussion

The results in Table I show that the rate of alkaline hydrolysis, as determined by formation of ammonia alone, is dependent on the hydrolysis of the intermediate amide. An induction period in the rate is observed, although the velocity constants approach the true values obtained by determination of total amide and ammonia. In the latter case, no induction period is evident and the reaction follows the bimolecular expression. The bimolecular constants recorded in Table II have been determined in this manner. The average deviation of the individual values from the recorded mean was about 1 to 2%.

Following the discussion outlined for the acid hydrolysis of propionitrile (11), the magnitude of the induction periods indicates that the relative rates of propionitrile and propionamide hydrolysis, over the concentration range,

TABLE I

DATA SHOWING NATURE OF THE INDUCTION PERIODS AND RELATIVE RATES OF PROPIONITRILE AND PROPIONAMIDE HYDROLYSIS

Concentration of alkali, normality	Temperature, °C.	Analytical procedure. A—ammonia only AA—amide and ammonia	$k \times 10^3$					
			NH ₃ * %					
			10 - 20	20 - 30	30 - 40	40 - 50	50 - 60	60 - 70
0.325	59.6	A	171	240	245		298	318
	59.6	AA	400	390	381	384	386	
0.650	39.5	A	27.3	36.2	44.2	47.2	48.0	
	39.5	AA	56.8	58.2	55.1	56.9	57.4	57.0
1.840	39.5	A	32.5 35.9	44.0	48.1	51.1		
	39.5	AA	59.6	58.7	59.4	60.0	59.1	

* Refers to runs analysed for ammonia only.

TABLE II

BIMOLECULAR VELOCITY CONSTANTS FOR THE HYDROLYSIS OF PROPIONITRILE IN SODIUM HYDROXIDE SOLUTIONS

Concentration of alkali, normality	Concentration of nitrile, normality	Temperature, °C.	$k \times 10^3$ hr. ⁻¹
0.325	0.2175	39.5	5.58
0.650	0.3020	39.5	5.69
0.650	0.2911	29.7	1.88
0.650	0.2716	49.6	15.1
0.650	0.3020	59.6	39.1
0.923	0.2721	39.5	5.66
1.840	0.3054	39.5	5.94
4.330	0.2963	39.5	5.96

are of the order of 1 : 10, within a factor of about two. This is confirmed by comparison of the present data with those of a number of investigators for the alkaline hydrolysis of amides (3, 6, 10). It is permissible to use data for acetamide hydrolysis, which are more numerous, for this purpose, since its velocity is within 10 to 20% of that for propionamide. Since the velocity of alkaline hydrolysis of both nitriles (Table II) and amides (4, 5) are independent of, or vary but slowly with, alkali concentration, the above approximate rate ratio should also apply over a wider concentration range than that considered here.

The induction period found in the present study, by determination of ammonia alone, agrees with the results of Reitz (12), but not with those of

Peskoff and Meyer (10) who did not observe it, although in both instances the reaction was followed by ammonia production. The reason for this discrepancy in the work of Peskoff and Meyer is not apparent. Furthermore, although their data indicate that the amide is hydrolysed faster than the nitrile (e.g., *propionamide* : *propionitrile* : : 0.1353 : 0.00888 (1 *N* potassium hydroxide, 25° C.)), for some reason these authors conclude that only the velocity of amide hydrolysis can be determined by their measurements. Kilpi (7) has noted this discrepancy, and has pointed out that on the basis of their data the velocity of the slower nitrile reaction has been measured. The present work shows that at all alkali concentrations considered, analysis must be made for total amide and ammonia to determine the velocity of nitrile hydrolysis.

The reaction velocity is essentially independent of alkali concentration (Table II) within the range considered and does not decrease at concentrations above 0.8 *N*, as has been reported by Reitz. The rate behaviour of the alkaline hydrolysis differs markedly from that in acid solution, where a very rapid increase in rate with acid concentration was found (11).

The data at 0.65 *N* alkali give an activation energy of 20,300 cal., obtained from the Arrhenius line. Calculation of the results of Peskoff and Meyer, for a range of 7° C. in 1 *N* potassium hydroxide, yields the approximate value 18,500 cal. for propionitrile and 19,100 for acetonitrile. Had circumstances permitted, it would have been desirable to find the activation energy at higher alkali concentrations, to determine whether it is dependent on concentration.

The activation energy for the alkaline hydrolysis of propionitrile is approximately 5000 cal. less than that for the acid hydrolysis, at the same catalyst concentration (8). This difference is in accord with the generally observed lowering of the activation energy for alkaline hydrolysis reactions as compared with acid hydrolysis (9, p. 253).

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ENZYME INHIBITION BY DERIVATIVES OF PHENOTHIAZINE

II. INHIBITION OF CHOLINESTERASE¹

By H. BRUCE COLLIER² AND DELLA E. ALLEN³

Abstract

The cholinesterase activity of horse serum is strongly inhibited by phenothiazine and by some phenothiazine alkyl-sulphonium salts. The magnitude of this inhibition is about equal to that produced by methylene blue and by acriflavine. Alkaline phosphatase and serum lipase are not affected.

The possible relation of this property of phenothiazine derivatives to certain nervous symptoms observed in treated pigs, and to insecticidal and anthelmintic action, is discussed.

The first paper in this series described the inhibition of catalase and of cytochrome oxidase by leuco-phenothiazine (3-hydroxy thiazine) (3), and a preliminary note has been published on the inhibition of succinic dehydrogenase by phenothiazine (3-oxythiazine) (4).

The well known effect of quaternary ammonium compounds on cholinesterase suggested that the phenothiazine oxidation products might exert a similar action, even though the N atom in these derivatives is not basic. Raventós (15) and Rentz (16) have reported an inhibition of the enzyme by methylene blue, and Massart and Dufait (12) have recently described inhibitions by this and other basic dyes. (Only an abstract of the last mentioned paper has been seen.)

The present paper describes a strong inhibition of horse-serum cholinesterase by phenothiazine and by sulphonium derivatives of phenothiazine. These compounds had no effect upon kidney phosphatase (at pH 9), or upon horse-serum lipase (acting upon tributyrin); therefore the inhibition does not apply to esterases in general.

Cholinesterase is the only *hydrolytic* enzyme thus far found susceptible to the action of phenothiazine derivatives.

Experimental

Method

The source of enzyme was fresh horse serum and the activity was measured manometrically in a Summerson differential manometer by a modification of the method of Stedman and Stedman (18).

A measured portion of the serum, usually 0.1 ml., was diluted to 2.0 ml. with a saline solution of the following composition: 0.85% sodium chloride, 0.025 M sodium bicarbonate, 0.001 M calcium chloride, 0.001 M manganese

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chloride. (This concentration of divalent ions was found to give maximum activity; potassium chloride up to 0.01 *M* had no effect.) The diluted serum was equilibrated for 30 min. at 37° C. with a 95%-nitrogen-5%-carbon-dioxide mixture, and was then mixed with 0.2 ml. of 2.5% acetylcholine bromide from the side arm of the reaction vessel. The final pH was 7.3, and the final substrate concentration was 0.01 *M*, which was found to give virtually as rapid hydrolysis as 0.05 *M* concentration.

The rate of carbon dioxide production was read differentially against a blank, identical with the above except for the addition of 10^{-8} *M* eserine* to inhibit the enzyme. Readings were taken every five minutes for 15 min. The rate of hydrolysis was found to be linear, and proportional to enzyme concentration, under these conditions; therefore the enzyme activity was expressed as μ l. of carbon dioxide in 15 min. at 37° C.

The inhibitors to be tested were dissolved in the saline in both vessels (having been first neutralized, if necessary), and were therefore in contact with the enzyme for 30 min. before the beginning of hydrolysis.

Preparations

Phenothiazone was prepared by oxidation of phenothiazine with ferric chloride (14). It was recrystallized from hot water and gave a melting point (corr.) of 165° C. Thionol (3-oxy-9-hydroxy thiazine) was prepared by the method of Bernthsen (2); it was partially purified by precipitation from alkaline solution with acid.

The S-methyl and S-ethyl sulphonium derivatives of phenothiazine were prepared by Kehrmann and Dardel's method (9), being isolated as the perchlorates. N-methyl phenothiazine was prepared by the method of Bernthsen (2).

Inhibition by Eserine

The inhibitory power of eserine (physostigmine), one of the most powerful inhibitors known, was determined under the conditions of these experiments, in order to make accurate comparison with the other inhibitors. The results may be summarized briefly as follows:

5×10^{-9} *M* eserine 20% inhibition

5×10^{-8} *M* eserine 66% inhibition

5×10^{-7} *M* eserine 91% inhibition

By interpolation it is found that 50% inhibition is produced by approximately 2.5×10^{-8} *M* concentration of eserine.

Effect of Phenothiazine Derivatives

The effect of methylene blue, phenothiazone, and thiazine methyl-sulphonium perchlorate on the enzyme is indicated in Tables I, II, and III. From these figures the concentrations necessary to produce 50% inhibition are found to be 1.2×10^{-8} *M*, 6.7×10^{-8} *M*, and 1.6×10^{-6} *M*, respectively.

* Physostigmine sulphate, kindly supplied by Merck & Co. Ltd., Montreal.

TABLE I
EFFECT OF METHYLENE BLUE ON CHOLINESTERASE

Concentration of dye, $M \times 10^7$	Enzyme activity, $\mu\text{l. CO}_2$	Inhibition, percentage
0	100	0
6	94	6
9	80	20
12	49	51
17	28	72
24	21	79
60	16	84
120	0	100

TABLE II
INHIBITION BY PHENOTHIAZONE

Concentration, $M \times 10^4$	Enzyme activity, $\mu\text{l. CO}_2$	Inhibition, percentage
0	158	0
1.7	129	18
3.3	121	23
6.7	79	50
16.7	31	80
48.0	0	100

TABLE III
INHIBITION BY PHENOTHIAZINE METHYL-
SULPHONIUM PERCHLORATE

Concentration, $M \times 10^6$	Enzyme activity, $\mu\text{l. CO}_2$	Inhibition, percentage
0	110	0
1.2	109	1
12.0	83	25
120.0	62	44
1200.0	17	85
12000.0	7	94
24000.0	0	100

Ethyl-sulphonium perchlorate gave an inhibition similar to that with the methyl derivative. Thionol and N-methyl phenothiazine were without effect.

Other Compounds

Indole, sulphanilamide, and *p*-hydroxylamino benzenesulphonamide were without effect upon the enzyme. Acriflavine (National Aniline and Chemical Co., New York), was found to be a powerful inhibitor, as indicated in Table IV.

TABLE IV
EFFECT OF ACRIFLAVINE ON CHOLINESTERASE

Concentration, $M \times 10^7$	Enzyme activity, $\mu\text{l. CO}_2$	Inhibition, percentage
0	109	0
5	99	9
50	65	40
100	39	64
500	4	96
1000	0	100

Discussion

The results of these experiments have been summarized in Table V, where the molar concentrations necessary to produce 50% inhibition of the activity of the serum cholinesterase are recorded. It may be concluded that the phenothiazine derivatives described are powerful inhibitors of cholinesterase, similar to strychnine (8) and morphine (1). Phenothiazone, which is not basic, is a somewhat weaker inhibitor than methylene blue, which contains a quaternary N atom, or the alkyl-sulphonium derivatives, which have a ternary S atom. In the case of the methyl-sulphonium salt, the great range of concentration observed, approximately 10^{-8} to 10^{-4} M, is worthy of note.

TABLE V
CONCENTRATIONS OF COMPOUNDS GIVING 50%
INHIBITION OF CHOLINESTERASE

Compound	Concentration	
	Molar	Mg. per litre
Eserine*	2.5×10^{-8}	0.007
Methylene blue	1.2×10^{-8}	0.45
Thiazine methyl-sulphonium ion*	1.6×10^{-8}	0.37
Acriflavine	6.6×10^{-8}	1.7
Phenothiazone	6.7×10^{-5}	14.0

* Calculated as the free base.

The physiological significance of these findings cannot be adequately assessed without further investigation. The recent reviews of Nachmansohn (13) and of Glick (6) discuss the role of cholinesterase in the mediation of

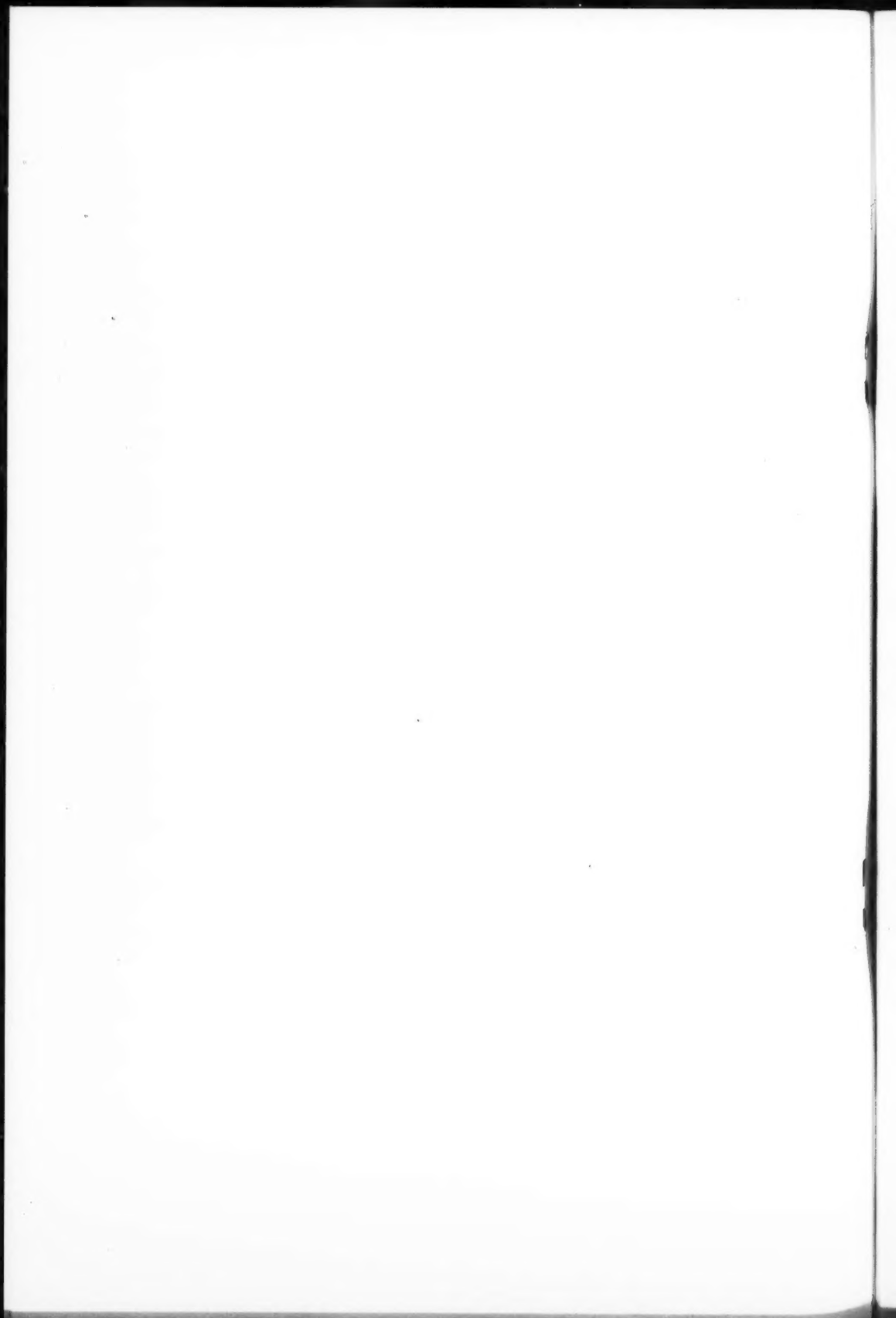
nerve impulses at synapses and neuromuscular junctions. It is therefore a possibility that phenothiazine derivatives may act upon the nervous system through inhibition of the cholinesterase. Or the compounds may be antagonistic to the action of acetylcholine, through a similarity of chemical structure (which would also explain the enzyme inhibition). These substances presumably have a pharmacological action similar to that of the "onium" salts, as described by Raventós (15) and by Ing (7).

Evidence for an apparent curariform action of phenothiazine may be found in the observation of H. O. J. Collier (5), that a one in ten million solution (probably oxidized to phenothiazone) increases the "block" in a neuromuscular preparation of the crab, *Carcinus moenas*. In addition, several groups of workers (10, 19) have reported nervous symptoms in pigs after phenothiazine treatment—partial posterior paralysis and inco-ordination.

Whether this effect of phenothiazine derivatives on cholinesterase is related to their insecticidal (17) or anthelmintic action is also a matter for speculation at the present time. McIlwain (11) has suggested that parasitic worms are narcotized by anthelmintic drugs, but the mechanism of this action has not yet been elucidated.

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